POLISH GYNECOLOGY

GINEKOLOGIA POLSKA

Edited since 1922

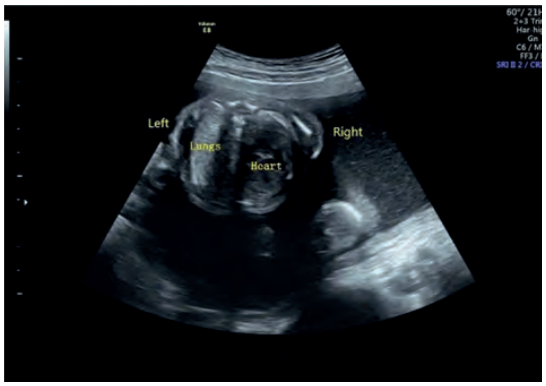
no 6/vol 95/2024

ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGÓW I POŁOŻNIKÓW
THE OFFICIAL JOURNAL OF THE POLISH SOCIETY OF GYNECOLOGISTS AND OBSTETRICIANS

IF: **1.2**, MNiSW: **40**

GINEKOLOGIA POLSKA 2024, VOL 95, NO 6, PAGES 419–508

ORIGINAL PAPERS



ISSN 0017–0011
e-ISSN 2543–6767

VIA MEDICA

VIA MEDICA

Top of the Top
Ginekologia i Położnictwo 2024

SZCZEGÓŁY

Gdynia, 30–31 sierpnia 2024 roku

Przewodniczący Komitetu Naukowego
prof. dr hab. n. med. Piotr Sieroszewski

www.topofthetopginekologia.viamedica.pl

PATRONAT MEDIALNY tvmed

PARTNER ikamed.pl

Konferencja jest skierowana tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t.j. Dz.U. z 2020 r. poz. 944).

POLISH GYNECOLOGY

GINEKOLOGIA POLSKA

ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGÓW I POŁOŻNIKÓW
THE OFFICIAL JOURNAL OF THE POLISH SOCIETY OF GYNECOLOGISTS AND OBSTETRICIANS

ISSN 0017–0011
e-ISSN 2543–6767

Ginekologia Polska is published monthly, twelve volumes a year, by VM Media Group sp z o.o.
73 Świętokrzyska St, 80–180 Gdańsk, Poland, phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60,
e-mail: redakcja@viamedica.pl, marketing@viamedica.pl, http://www.viamedica.pl

Editorial office address: Woman's Health Institute, School of Health Sciences, Medical University of Silesia in Katowice, 12 Medyków St, 40–752 Katowice, e-mail: ginpol@viamedica.pl

Indexed in: CrossRef, DOAJ, Index Copernicus, Polish Ministry of Science and Higher Education (40), POL-Index, Polish Medical Bibliography, PubMed, Science Citation Index Expanded (1.2), Scimago Journal Rank, Scopus, Ulrich's Periodicals Directory

Advertising. For details on media opportunities within this journal please contact the advertising sales department, 73 Świętokrzyska St, 80–180 Gdańsk, Poland, phone: (+48 58) 320 94 94, e-mail: marketing@viamedica.pl

Subscription for 2024. Printed institutional subscription — 12 issues for 1987.00 PLN. Printed individual subscription — 12 issues for 994.00 PLN. More details at: https://journals.viamedica.pl/ginekologia_polska/user/subscriptions

VI Forum Ginekologii i Perinatologii Praktycznej

Standardy postępowania w położnictwie i ginekologii

Łódź, 12–14 grudnia 2024 roku

SZCZEGÓŁY

Przewodniczący Komitetu Naukowego
prof. dr hab. n. med. Piotr Sieroszewski

www.forumginekologii.viamedica.pl

PATRONAT MEDIALNY

PARTNER

Konferencja jest skierowana tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t.j. Dz.U. z 2020 r. poz. 944).

POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGÓW I POŁOŻNIKÓW
THE OFFICIAL JOURNAL OF THE POLISH SOCIETY OF GYNECOLOGISTS AND OBSTETRICIANS

CONTENTS

VIA MEDICA

CLINICAL VIGNETTES

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2024, vol. 95, no. 6, 419–425

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.96205

The prognostic value of the post-treatment serum CA 125 level in patients with advanced endometrial cancer

Konrad P. Muzykiewicz[1], Ewa Iwanska, Karolina W. Pniewska, Maja Janeczek, Malgorzata Nowak-Jastrzab, Andrzej Kalamacki, Kazimierz Karolewski, Pawel Blecharz

Department of Gynecologic Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Branch in Cracow, Poland

ABSTRACT

Objectives: The goal of this analysis was to assess the prognostic value of the post-treatment serum CA 125 level in each member of a group of advanced endometrial cancer (aEC) patients in comparison to other clinical and pathological parameters.

Material and methods: Records of 266 patients treated at the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Cracow Branch between the years 2006 and 2018 were included in the study. Follow-up ranged from 1 to 138 months. Progression free survival (PFS) and overall survival (OS) were set as the endpoints. The tests chi-squared, Fisher, log-rank, Mann-Whitney, Kruskal-Wallis and Cox proportional hazard ratio were used for statistical analyses.

Results: In the analysed group, there was a significant association between an elevated serum CA 125 level following adjuvant treatment and shorter PFS and OS. After setting a cut-off value for CA 125 there was a statistically significant correlation between the marker and PFS and OS. Multivariate analysis indicated that the post-treatment serum CA 125 level is an independent prognostic factor of the course of aEC.

Conclusions: The post-treatment serum CA 125 level correlates significantly with both PFS and OS in each patient with aEC. The marker is an independent prognostic factor in this group. A low post-treatment level of the marker is a strong indicator of good 5-year survival, with 82% of patients reaching 5-year OS.

Keywords: advanced endometrial cancer; CA 125; post-treatment; adjuvant treatment

Ginekologia Polska 2024; 95, 6: 419–425

INTRODUCTION

Endometrial cancer (EC) accounted for 7% of all newly diagnosed malignancies in Poland in 2019 and is the most frequently diagnosed gynaecological cancer in developed countries. Though mostly diagnosed at an early stage, almost 20% of new reported cases were in advanced stages of the disease [International Federation of Gynecology and Obstetrics (FIGO) III and IV] [1–3]. Advanced endometrial cancer patients are a very heterogenous group, so individual approaches are required at each stage of the treatment.

CA 125 is a valid prognostic marker in the treatment of ovarian cancer, though its utility in EC patients has been studied mainly in pre-treatment settings. A high serum level of the protein prior to treatment corelates with a shorter overall survival (OS) rate, deeper myometrial invasion, lymphovascular space invasion, and nodal involvement. Unfortunately, due to a high number of false negative results, it has not been useful in planning the extent of operative procedures. There are analyses focused on building a prognostic model based on CA 125 level combined with other factors [4–15].

In addition, there is paucity of data on the significance of the post-treatment serum CA 125 level in aEC patients. Given the assay is widely available and low-cost it has potential as a valuable addition in planning individual follow-up for aEC patients.

Objectives

The aim of this study was to assess the prognostic utility of obtaining a serum CA 125 level at the end of primary treatment and to compare the marker's value in relation to other clinical and pathological parameters.

Corresponding author:
Konrad P. Muzykiewicz
Department of Gynecologic Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Branch in Cracow, 11 Garncarska St., 31–115 Cracow, Poland
e-mail: konrad.muzykiewicz@gmail.com

Received: 11.07.2023 Accepted: 23.11.2023 Early publication date: 19.12.2023

MATERIAL AND METHODS

This paper is a part of a larger retrospective analysis of medical data, where records of 266 patients treated at the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Cracow Branch, between the years 2006 and 2018 were included in the analysis. The last patient included in the analysis finished treatment in 2013, resulting in the minimal possible follow-up of five years. We performed a detailed analysis of the known EC prognostic factors, comorbidity, biochemical test results, the type, duration, and extent of surgery, the hospital where surgery was performed, stage and grade of cancer, its histology and Bokhman type, the type of adjuvant treatment (AT), and the treatment outcomes expressed using the RECIST criteria.

The patient files contained data on the pretreatment level of CA 125 only in about 44% of cases, mostly lacking information about the type of assay used, because the majority of patients were initially treated outside our Cancer Centre. Over 70% of the medical data files included information about the CA 125 level after treatment, all assessed on site at our Cancer Center using the Abbott Alinity I CA 125 II Reagent Kit assay, which is a chemiluminescent microparticle immunoassay (CMIA). Samples were taken 2–6 weeks after adjuvant treatment completion.

Progression-free survival (PFS) and OS were set as the endpoints and were both assessed at 12, 36 and 60 months. Due to insufficient data, the study patients were not differentiated according to cause of death.

Qualitative data was analysed by counting the number and percentage of each value. Comparison of variables was made using the chi-squared test, or, in cases of groups with low expected quantity, the Fisher detailed test. Kaplan-Meier curves were used to demonstrate the results of the analyses of qualitative features, and their comparison was made using the log-rank test. Quantitative data were analysed by counting mean value, standard deviation, median, quartiles, minimal value, and maximal value. Comparison of those variables was made using the Mann-Whitney test. In cases of three or more groups, comparisons were made using the Kruskal-Wallis test. Features which showed statistically significant differences were analysed post-hoc with the Dunn test. The Cox proportional hazard ratio model was used to examine the influence of quantitative features on PFS and OS. Hazard ratios (HR) and 95% confidence interval (CI) values were used in reporting the results. The cut-off values for tests based on quantitative data were determined using receiver operating characteristic (ROC) curves. The utility of each quantitative variable as a predictor was assessed using the area under the ROC curve (AUC). The level of statistical significance was set at a value of $p < 0.05$. The analyses were made using R software.

RESULTS

As mentioned before, this is a part of a larger analysis based on a group of 266 advanced endometrial cancer patients. Table 1 contains detailed demographic and clinical characteristics of this group, while data on progression-free survival, overall survival, and follow up are shown in Table 2 [16].

There was paucity of data on the serum CA 125 level prior to treatment because the patients were treated in various hospitals, and it was not assessed in most treatment centers before surgery.

The post-treatment data was far more complete and of better quality since most of the results came from a single laboratory in COOK. The mean value was 139.33 U/mL,

Table 1. Demographic and clinical characteristic of the study group

Demographic and clinical characteristic of the study group			
Feature	**Mean (SD)**	**Median (quartile)**	
		n	**[%]**
Age [years]	65.47 (9.75)	66 (59–73)	
	22–44	5	1.9
	45–64	112	42.1
	65+	149	56
BMI	30.13 (5.93)	29.8 (25.98–33.85)	
	Underweight (< 18.5)	1	0.4
	Normal (18.5–25)	44	16.5
	Overweight (25–30)	72	27.1
	Obese (> 30)	113	42.5
	No data	36	13.5
Comorbidity	Total	192	72.18
	Hypertension	169	63.53
	Diabetes mellitus	58	21.8
Diabetic patients treated with metformin	Yes	33	56.90
	No	24	41.38
	No data	1	1.72
FIGO 2009 stage	IIIA	75	28.2
	IIIB	93	34.96
	IIIC	63	23.68
	IVA	5	1.88
	IVB	8	3.01
	No data	22	8.27
Bokhman type	Type I	182	68.42
	Type II	70	26.32
	No data	14	5.26
Histological Grade	G1	34	12.78
	G2	126	47.37
	G3	57	21.43
	No data	49	18.42

SD — standard deviation; BMI — body mass index; FIGO — International Federation of Gynecology and Obstetrics

Table 2. Overall survival and progression-free survival in the study group

Number of patients	Number of events	Overall survival			
		12 months	36 months	60 months	Median [months]
266	106	87.23%	59.54%	49.59%	60
Number of patients	**Number of events**	**Progression-free survival**			
		12 months	36 months	60 months	Median [months]
266	122	71.02%	53.14%	45.42%	50

Post-treatment follow-up [months]							
N	Mean	SD	Median	Min	Max	Q1	Q3
266	36.94	31.63	25	1	138	11	61

SD — standard deviation

Table 3. Results of the analysis of selected variables in relation to overall survival (OS)

Results of the analysis of selected variables in relation to OS						
N	**Variable**	**Unit**	**HR**	**95% CI**		**p value**
1	Age at the moment of diagnosis	years	1.035	1.013	1.056	0.001
2	PLT before surgery	$10^3/\mu L$	1.003	1	1.005	0.02
3	LEU before AT	$10^3/\mu L$	1.073	1.046	1.101	< 0.001
4	PLT before AT	$10^3/\mu L$	1.005	1.003	1.006	< 0.001
5	NLR		1.06	1.034	1.086	< 0.001
6	PLR		1.001	1	1.002	0.011
7	Pre-treatment CA 125	U/mL	1	1	1.001	0.548
8	Post-treatment CA 125	U/mL	1.0003	1.0001	1.0005	0.001*
9	CA 125 pre-post treatment decline	U/mL	0.9998	0.9997	0.9999	0.029*

Variable	Number of patients	Number of deaths	Overall survival				p value
			12 months	36 months	60 months	Median [months]	
10. Histologic grade							
G1	34	8	93.21%	77.03%	64.19%	> max obs.	< 0.001
G2	127	40	92.22%	71.65%	63.24%	116	
G3	57	30	81.03%	37.82%	24.82%	25	
11. Bokhman type							
I	183	57	91.32%	69.08%	59.83%	116	< 0.001
II	71	42	75.24%	40.53%	28.43%	25	

HR — hazard ratio; CI — confidence interval

with the standard deviation at 786.84 U/mL, whereas the median was 16.5 U/mL, with the quartiles reaching 10.4–32.4 U/mL. We analyzed survival rates in the context of each patient's CA 125 level taken once after treatment, and in relation to many more variables. Results of the analysis for CA 125 and the variables which correlated significantly with PFS and/or OS are given in Tables 3 and 4.

Afterwards, the ROC curve was drawn for the post-treatment serum Ca125 level. The area under curve (AUC) value was 0.855 (Fig. 1). The optimal cut-off value for the examined parameter was assessed and identified as 21.38 U/mL with a sensitivity of 85.71% and specificity of 75.86%. This allowed us to distinguish two groups of aEC patients. The low-level group, with CA 125 values below the newly established cut-off point, and the high-level group with values above this level.

The results of the univariate analysis of the relation between dichotomized post-treatment CA 125 values (high — above cut-off, low — below cut-off) and OS and PFS are given in Table 5, and on Figure 2.

A multivariate analysis of the prognostic value of the post-treatment serum CA 125 level was then conducted with inclusion of known significant prognostic factors such as age, histological grade, Bokhman type. The results showed

Table 4. Results of the analysis of selected variables in relation to progression free survival (PFS)

Results of the analysis of selected variables in relation to PFS						
N	**Variable**	**Unit**	**HR**	**95% CI**		**p value**
1	Age at the moment of diagnosis	years	1.026	1.006	1.046	0.009
2	PLT before surgery	$10^3/\mu L$	1.003	1	1.005	0.027
3	LEU before AT	$10^3/\mu L$	1.064	1.043	1.085	< 0.001
4	PLT before AT	$10^3/\mu L$	1.004	1.003	1.005	< 0.001
5	NLR		1.054	1.03	1.078	< 0.001
6	PLR		1.001	1	1.002	0.036
7	Pre-treatment CA 125	U/mL	1	1	1.001	0.548
8	Post-treatment CA 125	U/mL	1.0003	1.0001	1.001	< 0.001*
9	CA 125 pre-post treatment decline	U/mL	0.9997	0.9995	0.9999	0.017*

Variable	**Number of patients**	**Number of events**	**Overall survival**				**p value**
			12 months	**36 months**	**60 months**	**Median [months]**	
10. Histologic grade							
G1	34	10	80.40%	73.09%	63.34%	> max obs.	< 0.001
G2	127	47	82.92%	65.18%	57.61%	93	
G3I	57	34	52.86%	27.11%	23.24%	15	
11. Bokhman type							
I	183	68	80.24%	62.69%	55.13%	93	< 0.001
II	71	46	48.74%	32.63%	24.16%	12	
11. Depth of myometrial invasion							
< 1/2	39	10	88.89%	75.00%	71.43%	> max obs.	0.018
> 1/2	163	69	80.54%	58.59%	47.84%	58	

HR — hazard ratio; CI — confidence interval

that the post-treatment serum CA 125 level was the only independent prognostic factors for both 5-year OS and PFS in the study group. Hazard ratios of a high post-treatment serum CA 125 level were 9.9 for death and 4.8 for progression. Detailed results of this analysis are presented in Table 6.

DISCUSSION

Most studies on the relevance of the serum CA 125 level in endometrial cancer patients relate to their values before treatment. Currently the ESMO-ESTRO-ESGO consensus does not recommend the routine use of this parameter during treatment and follow-up of patients with EC [17]. The largest metanalysis by Patsner and Won Yim comprises only 25 papers published internationally between 1984 and 2012, and they all deal with the significance of the preoperative serum CA 125 level. Their data indicate that 15–25% of patients whose disease was preoperatively qualified as confined to the uterus had an elevated serum CA 125 level prior to treatment, and in 75% of those cases there was nodal involvement or metastatic disease in the final pathologic report. There is a correlation between a high serum CA 125 level and shorter OS and PFS. Most of the papers in that

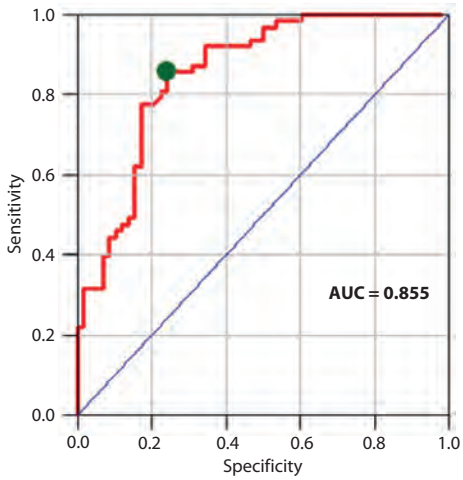


Figure 1. Receiver operating characteristic curve for the post-treatment serum CA 125 level; AUC — area under curve

metanalysis focused on the utility of CA 125 as a marker of nodal, peritoneal, or adnexal involvement. It seems to be a fairly good tool in this setting, indicating the necessity for a more radical surgical approach, with cut-off values ranging from 20 to 210 U/mL, and in most cases a range of

Table 5. Prognostic value analysis of the post-treatment serum CA 125 level as qualitative variable in relation to overall survival (OS) and progression free survival (PFS)

Prognostic value analysis of the post-treatment serum Ca125 level as qualitative variables in relation to OS and PFS							
Variable	Number of patients	Number of deaths or events	Overall survival				p value
			12 months	36 months	60 months	Median [months]	
1. OS							
CA 125 low-level	102	17	98.99%	89.92%	81.68%	> max obs.	0.001
CA 125 high--level	68	45	80.04%	36.44%	24.18%	26	
2. PFS							
CA 125 low-level	102	26	95.03%	84.07%	70.85%	> max obs.	0.001
CA 125 high--level	68	48	52.71%	26.50%	23.85%	15	

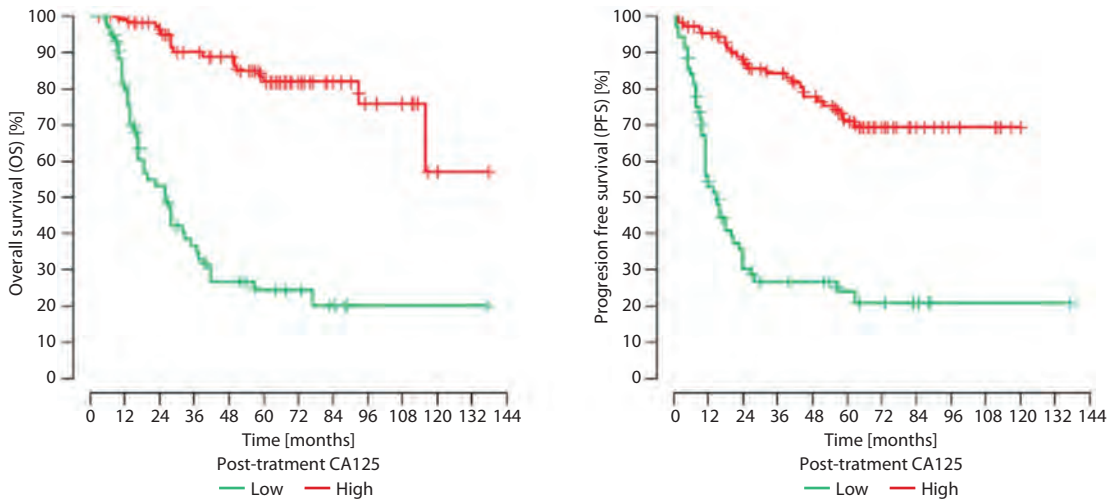


Figure 2. Kaplan-Meier overall survival and progression-free survival curves for the post-treatment serum CA125 level

35–40 U/mL. [4, 18] On the other hand, Hsieh and Chang emphasis that the decision not to perform lymphadenectomy cannot by based on a low serum CA 125 level, as more than 45% of results proved to be false negative. [8] There is also significant association between elevated preoperative CA 125 ≥ 21.2 U/mL and fibrinogen levels ≥ 2.58 mg/dL and lymphovascular space invasion (LVSI) as shown by Zhou and al. [9], whereas in a recent paper Shawn LyBarger and al. point that a pretreatment CA 125 level above 175 U/mL corelates significantly with LVSI and lymph node metastasis, with the effect peaking at levels above 222 U/mL. Researchers state that the increase in risk was the most prominent for patients having stage III/IV disease, reaching 1.67-fold. [10] Various prognostic models and algorithms based on CA 125 levels in compilation with HE4 and BMI [11], or immunohistochemical markers such as progesterone receptors and Ki67 [12] are being developed as diagnostic tools to facilitate pretreatment stratification of EC patients.

There are very few studies on the significance of the serum CA 125 level in advanced endometrial cancer. The first was in 1989 concerning a series of 15 aEC cases treated with either chemo or hormonal therapy. The reported post-treatment reduction in the CA 125 level, which had initially been elevated, was considered to be an indicator of a response to treatment. [13] A much larger group of 185 newly diagnosed aEC patients who underwent chemotherapy (paclitaxel + + carboplatin in 6 cycles) with or without radiotherapy as adjuvant treatment was studied by Hoskins and al. Many EC prognostic factors were taken into consideration along with the serum CA 125 level prior to treatment as well as following 3 cycles of chemotherapy. The results of the univariate analyses showed that CA 125 levels above 35 U/mL

Table 6. Multivariate analysis results

Multivariate analysis results					
Feature		**HR**	**95% CI**		**p value**
OS					
Age	[years]	1.02	0.988	1.053	0.226
Grade	G1	1	ref.		
	G2	1.123	0.403	3.131	0.825
	G3	1.459	0.484	4.403	0.503
Bokhman type	I	1	ref.		
	II	1.433	0.662	3.102	0.361
Post-treatment CA 125	Low	1	ref.		
	High	9.909	4.224	23.244	< 0.001*
PFS					
Age	[years]	1.022	0.99	1.054	0.176
Grade	GI	1	ref.		
	GII	1.336	0.539	3.31	0.532
	GIII	1.924	0.701	5.276	0.204
Bokhman type	I	1	ref.		
	II	1.504	0.738	3.066	0.261
Post-treatment CA 125	Low	1	ref.		
	High	4.778	2.421	9.429	< 0.001 *

HR — hazard ratio; CI — confidence interval

pretreatment, and above 24 U/ml after 3 cycles of treatment were significant markers of poorer prognoses. The serum CA 125 level exceeding 24 U/mL after 3 cycles of chemotherapy was found to be an independent negative prognostic factor in the multivariate analysis. Among patients with endometrioid aEC and a CA 125 level above 24 U/mL midway through chemotherapy, 13 out of 14 suffered a relapse, compared to 24 out of 56 in the low CA 125 group. The disease also relapsed in all patients in the Bokhman type II group with a high serum CA 125 level. The authors concluded that the marker is an excellent predictor of aEC recurrence and a mediocre predictor of non-recurrent disease [14].

In our own study, our analysis considered the serum CA 125 level before treatment, and after adjuvant treatment, and the difference between these two values. A statistically significant correlation between OS and PFS and the serum CA 125 level after AT was shown in the Cox analysis. There was also a significant correlation in the differences between pre- and post-treatment levels, but not in cases of the pre-treatment level alone. Though research shows that CA 125 assays are strongly related to each other and are clinically reliable for the quantification of serum CA 125, it is also advised against interchanging results from different methods [15]. Due to the low quality and quantity of data we had on the pretreatment serum CA 125 levels we put focus on the analysis of the post-treatment levels.

Further analyses of post-adjuvant treatment CA 125 level were performed dividing the variable to low- and high-level groups at the optimal cut-off of 21.4 U/mL (sensitivity 86%, specificity 76%). The logistic regression test showed a statistically significant ($p < 0.001$) correlation between the dichotomised CA 125 parameter and 5-year OS and PFS. The difference in survival in low- and high-level marker groups was considerable, with 5-year OS in the low-level group reaching 82%, which is 13% more than in the complete remission group based on the RECIST criteria. In the high-level group, 5-year OS was only 24%. The multivariate analysis results indicated that the serum CA 125 level after adjuvant treatment is an independent prognostic factor of OS (HR = 9.5) and of PSF (HR = 4.7) in advanced endometrial cancer. Our results are consistent with Hoskins' observation of the significance of low CA 125 level halfway through systemic treatment [14].

Unfortunately, we did not collect data on the Ca 125 levels during follow up, but there is evidence showing that CA 125 elevation can be an early marker preceding clinically evident recurrence [19].

CONCLUSIONS

A low level of post-treatment serum CA 125, defined as below 21.4 U/mL, is a strong marker of good 5-year survival in advanced endometrial cancer patients, with 82%

of patients alive after 60 months, and nearly 71% without recurrence. At the time of the emerging role of TCGA classification there are new ways to determine the prognosis of EC patients, but the availability of the new classification is still low due to the high cost of implementation. CA 125 is a cheap and easily accessible marker that can play an important role in planning individual follow-up schedules for aEC patients and counseling them about expected treatment outcome.

Article information and declarations

Data availability statement

Source data is available from the corresponding author.

Ethics statement

Does not apply due to the retrospective nature of the study.

Author contributions

Konrad Muzykiewicz — 60%, Ewa Iwańska — 5%, Karolina Pniewska — 5%, Maja Janeczek — 5%, Małgorzata Nowak-Jastrząb — 5%, Andrzej Kałamacki — 5%, Kazimierz Karolewski — 5%, Paweł Blecharz — 10%.

Funding

Own funding.

Conflict of interest

The authors declare no conflicts of interest.

Supplementary material

None.

REFERENCES

1. Didkowska J, Wojciechowska U, Olasek P, dos Santos FC, Michałek I. Nowotwory złośliwe w Polsce w 2019 roku. Narodowy Instytut Onkologii Państwowy Instytut Badawczy, Warszawa 2021.
2. GLOBOCAN 2018, Cancer Incidence Mortality and Prevalence Worldwide 2018. http://gco.iarc.fr/today (11.06.2023).
3. KRN – Krajowy Rejestr Nowotworów. http://onkologia.org.pl (11.06.2023).
4. Duk JM, Aalders JG, Fleuren GJ, et al. CA 125: a useful marker in endometrial carcinoma. Am J Obstet Gynecol. 1986; 155(5): 1097–1102, doi: 10.1016/0002-9378(86)90358-3, indexed in Pubmed: 3465243.
5. Patsner B, Mann WJ, Cohen H, et al. Predictive value of preoperative serum CA 125 levels in clinically localized and advanced endometrial carcinoma. Am J Obstet Gynecol. 1988; 158(2): 399–402, doi: 10.1016/0002-9378(88)90163-9, indexed in Pubmed: 2449079.
6. Sood AK, Buller RE, Burger RA, et al. Value of preoperative CA 125 level in the management of uterine cancer and prediction of clinical outcome. Obstet Gynecol. 1997; 90(3): 441–447, doi: 10.1016/s0029-7844(97)00286-x, indexed in Pubmed: 9277659.
7. Hsieh CH, ChangChien CC, Lin H, et al. Can a preoperative CA 125 level be a criterion for full pelvic lymphadenectomy in surgical staging of endometrial cancer? Gynecol Oncol. 2002; 86(1): 28–33, doi: 10.1006/gyno.2002.6664, indexed in Pubmed: 12079296.
8. Hsieh CH, ChangChien CC, Lin H, et al. Can a preoperative CA 125 level be a criterion for full pelvic lymphadenectomy in surgical staging of endometrial cancer? Gynecol Oncol. 2002; 86(1): 28–33, doi: 10.1006/gyno.2002.6664, indexed in Pubmed: 12079296.
9. Zhou X, Wang H, Wang X. Preoperative CA125 and fibrinogen in patients with endometrial cancer: a risk model for predicting lymphovascular space invasion. J Gynecol Oncol. 2017; 28(2): e11, doi: 10.3802/jgo.2017.28.e11, indexed in Pubmed: 27894164.
10. Shawn LyBarger K, Miller HA, Frieboes HB. CA125 as a predictor of endometrial cancer lymphovascular space invasion and lymph node metastasis for risk stratification in the preoperative setting. Sci Rep. 2022; 12(1): 19783, doi: 10.1038/s41598-022-22026-1, indexed in Pubmed: 36396713.
11. Knific T, Osredkar J, Smrkolj Š, et al. Novel algorithm including CA-125, HE4 and body mass index in the diagnosis of endometrial cancer. Gynecol Oncol. 2017; 147(1): 126–132, doi: 10.1016/j.ygyno.2017.07.130, indexed in Pubmed: 28735628.
12. Yang B, Shan B, Xue X, et al. Predicting Lymph Node Metastasis in Endometrial Cancer Using Serum CA125 Combined with Immunohistochemical Markers PR and Ki67, and a Comparison with Other Prediction Models. PLoS One. 2016; 11(5): e0155145, doi: 10.1371/journal.pone.0155145, indexed in Pubmed: 27163153.
13. Patsner B, Tenhoppen DJ, Mann WJ. Use of serum CA-125 levels to monitor therapy of patients with advanced or recurrent endometrial carcinoma. Eur J Gynaecol Oncol. 1989; 10(5): 322–325, indexed in Pubmed: 2806320.
14. Hoskins PJ, Le N, Correa R. CA 125 normalization with chemotherapy is independently predictive of survival in advanced endometrial cancer. Gynecol Oncol. 2011; 120(1): 52–55, doi: 10.1016/j.ygyno.2010.09.014, indexed in Pubmed: 20947152.
15. Davelaar E, Kamp Gv, Verstraeten R, et al. Comparison of seven immunoassays for the quantification of CA 125 antigen in serum. Clinical Chemistry. 1998; 44(7): 1417–1422, doi: 10.1093/clinchem/44.7.1417.
16. Muzykiewicz KP, Iwanska E, Janeczek M, et al. The analysis of the prognostic value of the neutrophil/ lymphocyte ratio and the platelet/lymphocyte ratio among advanced endometrial cancer patients. Ginekol Pol. 2021; 92(1): 16–23, doi: 10.5603/GP.a2020.0164, indexed in Pubmed: 33448001.
17. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. Int J Gynecol Cancer. 2016; 26(1): 2–30, doi: 10.1097/IGC.0000000000000609, indexed in Pubmed: 26645990.
18. Patsner B, Yim GaW. Predictive value of preoperative serum CA-125 levels in patients with uterine cancer: The Asian experience 2000 to 2012. Obstet Gynecol Sci. 2013; 56(5): 281–288, doi: 10.5468/ogs.2013.56.5.281, indexed in Pubmed: 24328017.
19. Pennington K, Reynolds R. Usefulness of serial CA-125 levels in surveillance of endometrial cancer. Gynecologic Oncology. 2011; 120: S97, doi: 10.1016/j.ygyno.2010.12.231.

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2024, vol. 95, no. 6, 426–433

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.98046

Clinical use of redox biomarkers for diagnosis of male infertility

Marek Szymanski[1–3], Radoslaw Janicki[2, 3], Piotr Kaminski[4], Karolina Wasilow[2], Jaromir Soltysiak[5], Robert Szyca[6], Angelika Szymanska[7], Marcin Arabik[8]

[1]Department of Obstetrics and Gynecology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

[2]NZOZ Medical Center, Clinic of Infertility Treatment "Genesis", Bydgoszcz, Poland

[3]Gynecology and Oncological Gynecology Ward, 10th Military Research Hospital and Polyclinic, IPHC, Bydgoszcz, Poland

[4]Department of Ecology and Environmental Protection, Department of Medical Biology and Biochemistry, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Bydgoszcz, Poland

[5]"Solmed Medical" Center Chojnice, Poland

[6]Clinic of Surgery and Oncological Surgery, 10th Military Research Hospital and Polyclinic, IPHC, Bydgoszcz, Poland

[7]The National Institute of Medicine of the Ministry of Interior and Administration, Warsaw, Poland

[8]Gynecology, Obstetrics and Pregnancy Pathology Department, Multi-speciality City Hospital, Bydgoszcz, Poland

ABSTRACT

Objectives: The aim of the study was to analyze the activity of antioxidant enzymes (glutathione reductase, catalase, superoxide dismutase) and malondialdehyde (MDA) levels in a population of men with abnormal semen parameters and in a population of men diagnosed with normozoospermia.

Material and methods: This study was performed using data collected at the Infertility Treatment Clinic ‚Genesis', Bydgoszcz, Poland, between 1 January 2011 and 31 December 2017. A total number of 455 men meeting the inclusion criteria were selected and divided into the control group (234 men) and the infertility group (221 men). The activities of superoxide dismutase (SOD), catalase (CAT), and glutathione reductase (GR) were measured using ready-made kits; lipid peroxidation intensity was determined by the thiobarbituric acid method.

Results: No statistically significant differences were found for activity of SOD, GR, CAT between the groups. MDA values measured in the serum of patients in the healthy group were higher than in the group with semenological disorders.

Conclusions: Although our study did not demonstrate the usefulness of the above blood tests, further studies are needed to explore the potential use of assessing redox parameters to develop new diagnostic and therapeutic approaches for male infertility.

Keywords: male infertility; oxidative stress; reactive oxygen species; superoxide dismutase; catalase; glutathione reductase; MDA; antioxidant defense

Ginekologia Polska 2024; 95, 6: 426–433

INTRODUCTION

According to the World Health Organization [1], infertility refers to the biological inability of an individual to achieve pregnancy following at least 12 months of unprotected intercourse [2, 3]. It has been estimated that approximately 15% of couples face some form of infertility and among them, male factor infertility plays a role in nearly 30–50% of all infertile couples [4, 5]. Male infertility diagnosis is commonly based on standard semen parameters analysis [6], according to the WHO guidelines, nevertheless, a large proportion of infertile males does not receive a clear diagnosis, considering them as idiopathic or unexplained cases [7, 8].

Epidemiological predictions indicate that the number of infertile couples will increase. In developed countries, the problem of primary infertility is more frequent, while

Corresponding author:
Marcin Arabik
Gynecology, Obstetrics and Pregnancy Pathology Department, Multi-speciality City Hospital, Bydgoszcz, Poland
e-mail: lekarz.arabik@gmail.com

Received: 26.03.2023 Accepted: 20.04.2023 Early publication date: 9.08.2023

developing countries, more often face the problem of secondary infertility. The infertility rate is not the same in each country, and it is determined by many factors, including civilization factors. In developed countries, it ranges between 10% and 12% [1].

According to forecasts, Poland's population will shrink by more than 10% over the next three decades, and such a drastic decline in population will be mainly due to declining birth rates. Obviously, this is influenced not only by the biological ability to reproduce, but also by the desire for parenthood or economic considerations. Nevertheless, making it possible to satisfy the need for an offspring through proper prevention, diagnosis and treatment of infertility should be one of the priorities of modern medicine, not only for the sake of future parents, but for the entire population. The modern model of life promoting the delay of procreative plans, fraught with a great deal of stress, as well as increasingly unfavorable environmental conditions, exacerbate the problem of infertility, posing a very great challenge to reproductive medicine [9].

Diagnosis of the causes of infertility should be carried out simultaneously in both partners. Male fertility is a direct result of the process of spermatogenesis, which involves the continuous production of sperm by the spermatogenic epithelium. It occurs in the spermatogenic tubules of the male gonad and lasts about 74 days [10]. It is known that a huge role in the regulation of physiological processes, including spermatogenesis, is played by health status, *i.e.*, the co-occurrence of conditions both related to the genitourinary system and other systemic dysfunctions. In recent years, the results of numerous studies have repeatedly confirmed the existence of a close relationship between male infertility and their general health status. The occurrence of certain conditions may be related to genetic and/or environmental factors [3, 11–14].

Oxidative stress

Every healthy organism has complex mechanisms whose role is to detoxify reactive oxygen species (ROS). An imbalance between ROS and the body's antioxidant mechanisms can result in sperm damage and loss of conceptus by the negative effects of ROS on sperm function and metabolism, mainly in affecting the processes of capacitation and the acrosomal reaction. During chronic oxidative stress, there is an increase in the amount of oxidized proteins in male gametes, which leads to changes in the structure of the membrane proteins of the sperm head and vitellum. Excessive exposure to ROS significantly reduces male fertility due to damage to sperm cell membranes [3].

Due to their high reactivity, oxygen free radicals, produced in excess, can have a very negative effect on the body. The consequence of this process, when antioxidant defense fails and physiological concentrations of ROS are exceeded, is a condition called "oxidative stress" [15, 16]. Oxidative stress is considered a major etiology for male infertility, more specifically idiopathic infertility. Large proportion of infertile males does not receive a clear diagnosis, considering them as idiopathic or unexplained cases [7].

The analysis of semen parameters according to the WHO guidelines represents, currently, the gold standard for male infertility diagnosis. Several studies showed that ROS-induced sperm oxidation can result in sperm quality alterations, leading to a decrease in sperm fertilizing potential [17–19].

The adverse effects of oxidative stress on sperm function represent a new direction of research into the mechanisms responsible for male infertility [20–22]. Based on the findings presented in the literature, the need to develop new diagnostic methods for male infertility was observed. Along with the assessment of oxidative stress in a seminal fluid, monitoring the redox status of blood could provide a new potential and less invasive practice for clinicians to assess the ability to conception [8]. The redox parameters studied could be useful for developing new therapeutic strategies based on antioxidant supplementation to reduce systemic oxidative stress in patients with infertility, improving the diagnostic process and possible treatment of male infertility and ultimately the success of assisted reproductive technology (ART) [8].

Assays for oxidative stress detection may suggest new biochemical approaches to improve male infertility diagnosis and management, using simple, fast and less expensive techniques [17].

The aim of the study was to analyze the activity of antioxidant enzymes (glutathione reductase, catalase, superoxide dismutase) and malondialdehyde levels in the population of men with abnormal semen parameters and in men diagnosed with normozoospermia and evaluating their usefulness of these determinations in the diagnosis of male infertility.

Atioxidant defense

Both enzymatic and non-enzymatic components of antioxidant defense are involved, with non-enzymatic mechanisms considered complementary elements, while antioxidant enzymes play a major role in the overall process. The most important antioxidant enzymes include superoxide dismutase (SOD), glutathione reductase (GR), and catalase (CAT). These enzymes are interrelated, cooperating to directly neutralize free radicals, reactivate non-enzymatic components of antioxidant defense, inhibit lipid peroxidation, and repair damaged molecules and destroy those that could not be repaired [23].

Superoxide dismutase (SOD)

Superoxide dismutase is the body's main defense mechanism against the toxic effects of peroxides. It catalyzes the breakdown of superoxide anions to hydrogen peroxide and molecular oxygen. Mitochondria, whose DNA is highly susceptible to free radical attack, must be protected by an efficient superoxide dismutase mechanism. Disruption of the activity of this enzyme can expose the cell to increased attack by ROS, which can damage genetic material, leading to mutations [24].

Catalase (CAT)

Catalase is the main line of defense against highly reactive hydrogen peroxide and is involved in its breakdown into water and oxygen. The enzyme exhibits CAT activity at high concentrations of hydrogen peroxide, causing its breakdown. In contrast, at low concentrations of H2O2, CAT exhibits peroxidase activity, participating in the oxidation of compounds such as methanol, ethanol, formates, nitrites and quinones.

Catalase, by converting hydrogen peroxide, does not generate additional free radicals, which protects cells from other reactive oxygen species. Oxygen from the breakdown of H2O2 can be further utilized in other metabolic processes [24]. This enzyme, by breaking down hydrogen peroxide, reduces the intensity of oxidative stress, and has a compensatory effect against oxidative damage.

Catalase, an enzyme that protects cells from the toxic effects of hydrogen peroxide, has been implicated in mutagenesis, carcinogenesis, inflammation and protection from apoptosis. It is thought that the enzyme's activity may be reduced by prolonged exposure of patients' cells to oxidative stress.

Glutathione reductase (GR)

Glutathione reductase is an enzyme whose role is to restore oxidized glutathione (GSSG) to its reduced form (glutathione regeneration), using electrons derived from NADPH. The reaction catalyzed by reductase proceeds in a sequential census or ping-pong method, which is influenced by the concentration of the oxidized form of glutathione and NADP+. By catalyzing the GSH/GSSG cycle, glutathione reductase prevents excessive accumulation of reactive oxygen species and the formation of associated oxidative damage. This is related to the fact that glutathione disulfide - formed in the reaction catalyzed by glutathione peroxidase — is a cell-damaging compound (capable of inactivating cellular proteins), while it is glutathione in its reduced form that shows antioxidant potential and reacts with hydrogen peroxide [25].

Malondialdehyde (MDA)

Reactive oxygen species are involved in the free radical oxidation of unsaturated fatty acids in lipids, the so-called lipid peroxidation [26]. The end products of lipid peroxidation can be low molecular weight, three-carbon malondialdehyde (MDA) and other aldehydes and hydroxyaldehydes. Malondialdehyde is the most important stable product of lipid peroxidation. Malondialdehyde is one of the most mutagenic products of lipid peroxidation. It reacts with DNA to form premutagenic lesions [27]. Numerous studies show that MDA is one of the primary factors informing about the ongoing processes of lipid peroxidation, and thus indicating the intensification of oxidative stress.

Elevated levels of free radicals intensify lipid peroxidation and increase MDA production. It is believed that concentration of malondialdehyde may be an indicator of increased oxidative stress and antioxidant status of the body [28].

MATERIAL AND METHODS

Research was undertaken following the Guidelines of the European Union Council and the current laws in Poland, according to the Bioethical Commission of the Collegium Medicum of Nicolaus Copernicus University in Torun, Poland. Samples were collected under permit KB 674/2010; No. KB 427/2014 and No. KB 365/2015.

Semen analysis

We conducted semen testing from 2011 to 2017 at the NZOZ Medical Center - Infertility Treatment Clinic 'Genesis', a center accredited by the Polish Ministry of Health as a Medically Assisted Reproductive Center, Cell and Embryo Bank.

Semen testing was performed on each patient-participant in the study. Prerequisites included a 2–7.day period of sexual abstinence. During semen evaluation, macroscopic evaluation was performed, with determination of volume (mL) and reaction (pH) of semen, microscopic evaluation, with determination of concentration (million/mL), motility (type A fast progressive movement (%); type B slow progressive movement (%); type C non-progressive movement (%); type D no movement (%); type A + B progressive movement, A + B + C total movement) evaluation was performed in a Makler chamber and using a light microscope. The morphology (%) of spermatozoa in the semen was also evaluated.

In the semenological analysis, the ejaculate was treated as normal according to WHO 2010 criteria. Based on the results of the standard semen evaluation, the study participants were divided into two groups:

— the control group consisted of 162 patients in whom there were no abnormalities in the analyzed semen

parameters (semen volume, concentration of sperm in semen, motility and morphological structure of sperm) — normozoospermia (WHO 2010);

— the infertility group consisted of 159 men with semen abnormalities applied to oligozoospermia, asthenozoospermia, azoospermia, teratozoospermia, necrozoospermia, combined oligozoospermia- asthenozoospermia-teratozoospermia OAT II, OAT III, cryptozoospermia, polyzoospermia, cryptoteratozoospermia, leukospermia or combined disorders.

Antioxidant enzyme activity and lipoperoxidation intensity

In addition to semen, whole blood of about 15 mL and blood serum were collected from patients approx. 1.5 mL. To obtain the serum, the blood was drawn into "clot" type tubes. The serum was obtained by centrifugation at 3500 rpm for 10 minutes. The serum and semen were separated into Eppendorf-type tubes. The material was transported to the laboratory of the Department of Ecology and Environmental Protection, Collegium Medicum of Nicolaus Copernicus University in Torun, Poland. The whole blood was stored at -80 deg C, as was serum. Semen, on the other hand, was stored in liquid nitrogen.

Determination of antioxidant enzyme activity (SOD, CAT, GR), and lipoperoxidation intensity (MDA) in blood serum was carried out using ready-to-use kits from Cayman Chemicals Co. and Wuhan EIAab Science.

Activity of superoxide dismutase

Serum SOD activity was determined using a standardized Superoxide Dismutase Assay Kit (Cayman Chemical Co. Item No. 706002). The analyses were performed on 96-well plates according to the methodology provided by the manufacturer. Two hundred microliters of radical detector solution (tetrazolium salt solution) were added to the samples and 10 µL of standards. The reaction was started by adding 20 µL of xanthine oxidase solution to all wells. The plate was carefully shaken for several seconds to mix the reaction components and incubated on a shaker for 20 min at room temperature. The absorbance was measured at 450 nm using a plate reader (Multiskan RC Version 6.0, Lab systems). The SOD activity in the samples was calculated from the standard curve and expressed in $U \cdot mL^{-1}$.

Glutathione reductase activity

Glutathione reductase activity in serum was tested using Cayman Chemical's off-the-shelf Glutathione Reductase Assay Kit. The assay was based on measuring the efficiency of NADPH oxidation. The oxidation of NADPH to NADP+ carries a decrease in absorbance at 340nm, which is directly proportional to the GR activity in the sample. Assay Buffer was diluted with high purity water to obtain a buffer containing 50 mM potassium phosphate, pH 7.5, with 1 mM EDTA. Sample Buffer after dilution with high-purity water contained 50 mM potassium phosphate, pH 7.5, with 1 mM EDTA and 1 mg* mL-1 BSA. In this form, it was used to dilute the following reagents. Glutathione reductase control containing GR isolated from baker's yeast was diluted with Sample Buffer (10 µL of enzyme + + 990 µL of Sample Buffer) and placed on ice (according to the accompanying instructions, 20 µL of diluted enzyme when added to the well causes a decrease in absorbance at a rate of about 0.04 absorbance units per minute under standard reaction conditions). GR NADPH — supplied as a lyophilized powder was dissolved in high-purity water. GR GSSG (9.5 mM GSSG solution) was ready to use without prior preparation. The assay was performed in a 96-well plate, the scheme of which was analogous to the GPx assay.

Catalase activity

Serum CAT activity was determined using a standardized Catalase Assay Kit (Cayman Chemical Co. Item No. 707002). The analyses were performed on 96-well plates according to the methodology provided by the manufacturer. Assay Buffer (100 µL) and methanol (30 µL) were added to the samples, to the standards, and to 20 µL of bovine liver catalase, which served as a positive control. The reaction was started by adding 20 µL of hydrogen peroxide to all wells. The plate was incubated for 20 min at room temperature. To terminate the reaction, 30 µL of potassium hydroxide was added to samples, standards, and positive controls, followed by 30 µL of chromogen (Purpald). The plate was then incubated on a shaker for 10 min at room temperature. Next, 30 µL of potassium periodate was added to all wells. The plate was incubated on a shaker for 5 min at room temperature. The absorbance at 540 nm was measured using a plate reader (Multiskan RC Version 6.0, Lab systems). The CAT activity in the samples was calculated from the standard curve and expressed in $U \cdot mL^{-1}$.

Analysis of malondialdehyde concentration

Malondialdehyde concentration, indicating the intensity of lipid peroxidation processes, was measured by the method of Rice-Evans et al. (1991) [29] as modified by Atmaca et al. (2004) [30]. To the analyzed serum and one of the controls containing 200 µL of distilled water, the following reagents were added: 20 µL of 2% BHT (butylhydroxytoluene) in ethanol, 1 mL of 15% TCA (trichloroacetic acid) in 0.25 M HCl, and 1 mL of 0.37% TBA (thiobarbituric acid) in 0.25 M HCl. In the second control sample TBA was replaced by 1 mL of distilled water. The samples were vortexed and heated in a water bath at 100°C for 10 min. After cooling, the samples were centrifuged. The absorbance in the supernatant was measured at 535 nm against distilled water as control. The obtained absorbances were corrected by subtracting the

absorbances of controls with TBA replaced by distilled water. Malondialdehyde concentration in the samples was calculated using the absorbance coefficient (156 mmol−1•cm−1). The concentration was expressed in μM.

Statistical analysis

Statistical analyses were performed with The R statistical package version 4.0.2. Regarding quantitative parameters, the results are displayed as minimum and maximum values, quartiles (Q1, Q3), medians, arithmetical averages and standard deviations. Data were analyzed for normal distribution. Those that did not exhibit normal distribution were analyzed with non-parametric tests (U-Mann-Whitney). Normally distributed data were compared with a Student-t test. Correlations were analyzed with Spearman rank correlation tests. The coefficient of significance was set at $\alpha < 0.05$ and statistical significance at $p < 0.05$ [31].

RESULTS

There were no statistically significant differences between the control and abnormal spermiogram groups in terms of antioxidant enzyme activity (SOD, CAT).

Malondialdehyde values and glutathione reductase activity measured in the serum of patients in the healthy group were higher than in the group with spermiogram disorders (Fig. 1).

DISCUSSION

Reactive oxygen species produces extensive protein damage, cytoskeletal modifications and inhibit cellular mechanisms. However, on the other hand ROS are fundamental mediators of physiological sperm function, such as signal transduction mechanisms that influence fertility. Reactive oxygen species can have positive effects on sperm and the concentration functions depending on the nature and the concentration of the ROS involved. They are necessary in regulating hyperactivation and the ability of the spermatozoa to undergo the acrosomal reaction [32].

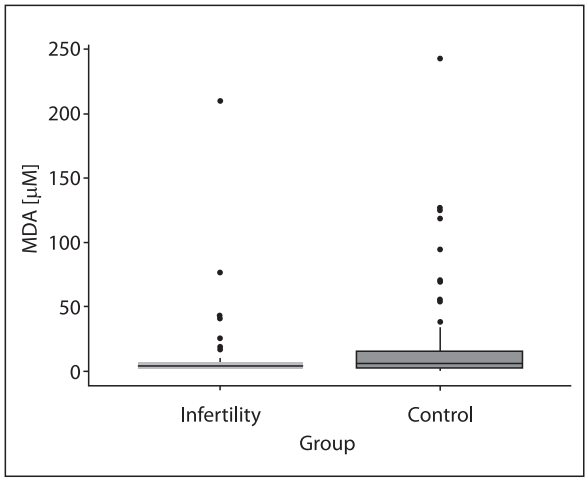


Figure 1. Malondialdehyde (MDA) concentration in the group of healthy and infertile patients

Impaired sperm activity, function and morphology can occur when levels of ROS or other free radicals are significantly elevated, while the body's antioxidant capacity is reduced [33, 34]. Elevated levels of ROS are found in 25–80% of infertile men, which is further associated with low levels of antioxidants in semen for men without fertility disorders [33, 35]. Reactive oxygen species causes a decrease in semen parameters by damaging sperm DNA or by initiating lipid peroxidation in membrane structures, which has a negative impact on sperm motility and the ability to fertilize oocytes [36]. Sources of ROS are many. These include activated leukocytes from inflammatory processes, immature spermatogenesis cells with abnormal morphology, coexistence of varicocele or cryptorchidism. In addition to factors independent of the patient, lifestyle, addictions, environmental and occupational exposures, and diet are also sources of excessive ROS [34].

Studies over the past two decades provide significant evidence to support the concept that excessive production of ROS is one of the causes of abnormal semen parameters and sperm damage [3, 11–14]. Male germ cells are extremely vulnerable to oxidative stress as the sperm membrane is rich in unsaturated fatty acids and lacks the capacity for DNA repair. Spermatozoa are particularly susceptible to ROS-induced damage because their plasma membranes contain large quantities of polyunsaturated fatty acids (PUFA) and their cytoplasm contains low concentrations of the scavenging enzymes [27].

As spermatozoa has relatively low intracellular antioxidant activity, the enzymatic antioxidants present in seminal plasma, meaning SOD, CAT and GR, therefore play a very important role. In addition, several non-enzymatic antioxidants also contained in seminal plasma, such as ascorbic acid, uric acid and alpha-tocopherol, play a supporting function [37].

Sperm antioxidant defense is enhanced by MDA, which, as a breakdown product formed during lipoperoxidation, is one of the primary factors determining the intensity of this process by which it determines the severity of oxidative stress [38, 39]. The phenomenon of lipid lipoperoxidation disrupts the basic parameters of sperm, causing impairment of membrane integrity, motility and overall sperm metabolism [40].

Excess production of ROS can trigger the phenomenon of lipid peroxidation through non-enzymatic or enzymatic mechanisms. Lipoperoxidation products exhibit high biological activity and are capable of inducing cell death. Undoubtedly, the balance between ROS generation and elimination is a decisive factor. Therefore, under conditions

Table 1. Malondialdehyde (MDA) concentration and superoxide dismutase (SOD), catalase (CAT), and glutathione reductase (GR) activities in the infertility group (n = 159) and in the control group (n = 162)

Parameter	Control group							Infertility group							
	x	SD	Min	Q_1	Me	Q_3	Max	x	SD	Min	Q_1	Me	Q_3	Max	p value*
MDA [μm]	22.65	42.5	0.21	2.68	5.21	14.59	242	10.94	30.66	0.21	1.8	2.9	6.2	209	0.0136
CAT activity [nmol·min^{-1}·mL^{-1}]	58.98	91	2.46	23.51	40.4	69.22	1011.6	81.82	137.61	0.0	28.18	40.9	100.35	159.9	0.7248
SOD activity [U·mL^{-1}]	2.47	2.59	0.0	0.49	1.57	3.89	14.59	8.04	34.03	0.01	0.82	2.6	4.22	227.95	0.0508
GR activity [U·mL^{-1}]	26.09	17.6	0.0	14.43	20.94	33.11	89.14	28.48	24.74	1.7	13.41	19.7	38.2	114.61	0.0368

SD — standard deviation; Min — minimum value; Q — quartile; Me — medians; Max — maximum value; *Mann-Whitney U test

of limited lipoperoxidation, cell survival is promoted (the process itself stimulates the production of an "adaptive response", which manifests itself in the mobilization of antioxidant systems). In contrast, under toxic conditions (high levels of lipid peroxidation), the processes of apoptosis and cell necrosis are promoted [41].

Oxidative stress can be evaluated in different biological samples (plasma, serum, follicular/peritoneal/seminal fluid), obtaining an accurate picture of redox status. Blood and plasma redox status alterations have been reported in infertile men, as recently described in the study showing higher blood leukocytes ROS production, increased plasma lipid peroxidation (LPO) and reduced plasma total antioxidant capacity (TAC) in oligoasthenozoospermic men compared to healthy subjects [42]. In line with this, several findings also suggest that ROS-mediated sperm oxidation may induce cellular dysfunctions, affecting spermatozoa concentration, total number and motility [20, 43].

Although MDA levels may not be correlated with sperm DNA fragmentation and oxidation, suggesting that some fundamental parameters for sperm quality may remain independent of MDA [44], previous studies have emphasized the link between intense lipid peroxidation, elevated MDA levels, deteriorating sperm quality and overall reproductive potential [38, 39].

In these studies, it was found that higher levels of MDA in plasma and seminal fluid of infertile men correlated with semen parameters, thus indicating that redox status affects procreative capacity [38, 39, 45].

The data obtained in our study shows that serum MDA levels in men with normozoospermia were higher (22.65 μM) than in those with fertility disorders (10.94 μM, p = 0.013); (Tab. 1.). Our results are consistent with those of Kasperczyk et al. (2016) [46]. Morales et al. [47] note that elevated MDA levels can also be interpreted as a kind of adaptive mechanism. In some organisms, especially with undisturbed regulation of redox signaling, MDA can stimulate regulatory genes or even participate in cellular protection under oxidative stress. Therefore, transient increases in MDA may serve as a defensive signaling factor that participates in mobilizing antioxidant mechanisms to counter ROS. These suggestions led us to consider the temporary increases in MDA concentration as a protective mechanism rather than as an indicator of damage. This is an interpretation that may be valid for the healthy male controls analyzed in our study (Tab. 1). In addition, some key methodological aspects may determine the usefulness, or lack thereof, of the obtained results of MDA concentrations for specific analytical and research questions [47]. In the case of continuous exposure to oxidative stress, certain factors responsible for it tend to cause an increase in MDA concentrations in a dose-dependent manner. In such situations, the opposite effect can be observed with respect to the enzymatic activity of antioxidants, which can be significantly reduced [48].

In other published data, increased lipid peroxidation positively correlates with impaired spermatogenesis and reduced semen parameters and its marker MDA is elevated in infertile patients compared to patients without fertility disorders [49–51]. In other studies, MDA levels do not differ between fertile and infertile patients, moreover, it did not change under the influence of introducing additional antioxidant factors such as zinc supplementation [52]. With reference to the literature data, the result in terms of serum MDA levels in men with normozoospermia in the presented study does not seem controversial.

Shamsi et al. [53] found that blood levels of SOD and GSH positively correlated with sperm count and motility, while elevated MDA levels were associated with altered sperm morphology. Another study proves that plasma TAC significantly and positively correlated with both seminal fluid TAC and semen parameters [54], indicating that plasma redox status reflects the redox status of the seminal fluid microenvironment and sperm quality.

Our study proves that the assay of serum antioxidant enzyme activity (SOD, CAT), does not seem to be useful in the diagnosis of male infertility. There were no differences in the activity of these enzymes between the analyzed groups.

Although other authors have reported that the determination of antioxidant enzyme activity could be used to identify patients with oxidative stress and thus those who may be eligible for antioxidant treatment [55–57]. Further analyses and a comprehensive diagnostic and therapeutic consensus are needed.

CONCLUSIONS

It is known that oxidative stress is strongly associated with sperm dysfunction and represents a new pathological mechanism of male infertility [8, 20–22]. Numerous studies on this issue point to the need to develop new methods and diagnostic strategies for assessing male fertility. Along with assessing oxidative stress in seminal fluid, monitoring the redox status of blood could provide a new potential and less invasive practice for clinicians to assess sperm quality and fertilizing capacity. Although our study did not demonstrate the usefulness of the blood tests which were analyzed, further studies are needed to explore the potential use of assessing redox parameters to develop new diagnostic and therapeutic approaches for male infertility.

An interesting aspect of our study is the observed increase in GR in the group of patients with infertility, which requires further analysis, as we did not find studies on this issue in the available literature.

Article information and declarations

Data availability statement

The data presented in this study are available on request from the corresponding author.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Bioethical Commission of the Collegium Medicum of Nicolaus Copernicus University in Torun, Poland. Samples were collected under permit KB 674/2010; No. KB 427/2014 and No. KB 365/2015.

Funding

This research received no external funding.

Author contributions

M.S. and K.W. — conceptualization; M.S. — methodology; J.S. — software; R.S. and P.K. — validation; J.S. and M.A. — formal analysis; M.S., K.W., R.S., R.J., P.K., J.S., A.S. and M.A. — investigation; M.S. — resources; K.W. — data curation; M.S. and K.W. — writing, original draft preparation; M.S., K.W. and M.A. — writing, review and editing; M.A. — visualization; K.W. — supervision; M.A. — project administration. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

1. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010; 16(3): 231–245, doi: 10.1093/humupd/dmp048, indexed in Pubmed: 19934213.
2. Aitken RJ. Impact of oxidative stress on male and female germ cells: implications for fertility. Reproduction. 2020; 159(4): R189–R201, doi: 10.1530/REP-19-0452, indexed in Pubmed: 31846434.
3. Aitken RJ, Drevet JR, Moazamian A, et al. Male infertility and oxidative stress: a focus on the underlying mechanisms. Antioxidants (Basel). 2022; 11(2), doi: 10.3390/antiox11020306, indexed in Pubmed: 35204189.
4. Wagner H, Cheng JW, Ko EY. Role of reactive oxygen species in male infertility: An updated review of literature. Arab J Urol. 2018; 16(1): 35–43, doi: 10.1016/j.aju.2017.11.001, indexed in Pubmed: 29713534.
5. Lotti F, Maggi M. Sexual dysfunction and male infertility. Nat Rev Urol. 2018; 15(5): 287–307, doi: 10.1038/nrurol.2018.20, indexed in Pubmed: 29532805.
6. Nallella KP, Sharma RK, Aziz N, et al. Significance of sperm characteristics in the evaluation of male infertility. Fertil Steril. 2006; 85(3): 629–634, doi: 10.1016/j.fertnstert.2005.08.024, indexed in Pubmed: 16500330.
7. Sharlip I, Jarow J, Belker A, et al. Best practice policies for male infertility. Fertil Steril. 2002; 77(5): 873–882, doi: 10.1016/s0015-0282(02)03105-9.
8. Mannucci A, Argento FR, Fini E, et al. The impact of oxidative stress in male infertility. Front Mol Biosci. 2021; 8: 799294, doi: 10.3389/fmolb.2021.799294, indexed in Pubmed: 35071326.
9. Jungwirth A, Giwercman A, Tournaye H, et al. European Association of Urology guidelines on male infertility: the 2012 update. Eur Urol. 2012; 62(2): 324–332, doi: 10.1016/j.eururo.2012.04.048, indexed in Pubmed: 22591628.
10. Griswold MD. Spermatogenesis: The Commitment to Meiosis. Physiol Rev. 2016; 96(1): 1–17, doi: 10.1152/physrev.00013.2015, indexed in Pubmed: 26537427.
11. Deepinder F, Cocuzza M, Agarwal A. Should seminal oxidative stress measurement be offered routinely to men presenting for infertility evaluation? Endocr Pract. 2008; 14(4): 484–491, doi: 10.4158/EP.14.4.484, indexed in Pubmed: 18558605.
12. Makker K, Agarwal A, Sharma R. Oxidative stress & male infertility. Indian J Med Res. 2009; 129(4): 357–367, indexed in Pubmed: 19535829.
13. Sabeti P, Pourmasumi S, Rahiminia T, et al. Etiologies of sperm oxidative stress. Int J Reprod Biomed. 2016; 14(4): 231–240, doi: 10.29252/ijrm.14.4.231.
14. Huang C, Cao X, Pang D, et al. Is male infertility associated with increased oxidative stress in seminal plasma? A-meta analysis. Oncotarget. 2018; 9(36): 24494–24513, doi: 10.18632/oncotarget.25075.
15. Saikolappan S, Kumar B, Shishodia G, et al. Reactive oxygen species and cancer: a complex interaction. Cancer Lett. 2019; 452: 132–143, doi: 10.1016/j.canlet.2019.03.020, indexed in Pubmed: 30905813.
16. Galadari S, Rahman A, Pallichankandy S, et al. Reactive oxygen species and cancer paradox: to promote or to suppress? Free Radic Biol Med. 2017; 104: 144–164, doi: 10.1016/j.freeradbiomed.2017.01.004, indexed in Pubmed: 28088622.
17. Agarwal A, Majzoub A. Laboratory tests for oxidative stress. Indian J Urol. 2017; 33(3): 199–206, doi: 10.4103/iju.iju_9_17, indexed in Pubmed: 28717269.
18. Dutta S, Majzoub A, Agarwal A. Oxidative stress and sperm function: a systematic review on evaluation and management. Arab J Urol. 2019; 17(2): 87–97, doi: 10.1080/2090598X.2019.1599624, indexed in Pubmed: 31285919.

19. Martins AD, Agarwal A. Oxidation reduction potential: a new biomarker of male infertility. Panminerva Med. 2019; 61(2): 108–117, doi: 10.23736/S0031-0808.18.03529-2, indexed in Pubmed: 30990283.
20. Agarwal A, Makker K, Sharma R. Clinical relevance of oxidative stress in male factor infertility: an update. Am J Reprod Immunol. 2008; 59(1): 2–11, doi: 10.1111/j.1600-0897.2007.00559.x, indexed in Pubmed: 18154591.
21. Hosseinzadeh Colagar A, Karimi F, Jorsaraei SG. Correlation of sperm parameters with semen lipid peroxidation and total antioxidants levels in astheno- and oligoasheno- teratospermic men. Iran Red Crescent Med J. 2013; 15(9): 780–785, doi: 10.5812/ircmj.6409, indexed in Pubmed: 24616785.
22. Agarwal A, Rana M, Qiu E, et al. Role of oxidative stress, infection and inflammation in male infertility. Andrologia. 2018; 50(11): e13126, doi: 10.1111/and.13126, indexed in Pubmed: 30569652.
23. Irato P, Santovito G. Enzymatic and non-enzymatic molecules with antioxidant function. Antioxidants (Basel). 2021; 10(4): 579, doi: 10.3390/antiox10040579, indexed in Pubmed: 33918542.
24. Sharma VK, Singh TG, Garg N, et al. Dysbiosis and Alzheimer's disease: a role for chronic stress? Biomolecules. 2021; 11(5): 678, doi: 10.3390/biom11050678, indexed in Pubmed: 33946488.
25. Druga twarz tlenu: wolne rodniki w przyrodzie. Wydawnictwo Naukowe PWN, Warszawa 2022.
26. Bhattacharya T, Dey PS, Akter R, et al. Effect of natural leaf extracts as phytomedicine in curing geriatrics. Exp Gerontol. 2021; 150: 111352, doi: 10.1016/j.exger.2021.111352, indexed in Pubmed: 33894308.
27. Kulbacka J, Saczko J, Chwiłkowska A. [Oxidative stress in cells damage processes]. [Article in Polish]. Pol Merkur Lekarski. 2009; 27(157): 44–47, indexed in Pubmed: 19650429.
28. Arya A, Chahal R, Rao R, et al. Acetylcholinesterase inhibitory potential of various sesquiterpene analogues for alzheimer's disease therapy. Biomolecules. 2021; 11(3): 350, doi: 10.3390/biom11030350, indexed in Pubmed: 33669097.
29. Rice-Evans C, Diplock AT, Symons MC. Techniques in free radical research. Elsevier, Amsterdam, London, New York, Tokyo 1991.
30. Atmaca M, Tezcan E, Kuloglu M, et al. Antioxidant enzyme and malondialdehyde values in social phobia before and after citalopram treatment. Eur Arch Psychiatry Clin Neurosci. 2004; 254(4): 231–235, doi: 10.1007/s00406-004-0484-3, indexed in Pubmed: 15309392.
31. Hill SA. Statistics. In foundations of anesthesia. In: Hemmings HC, Hopkins PM. ed. Foundations of anesthesia. Basic sciences for clinical practice. Elsevier 2006: 207–217.
32. Tafuri S, Ciani F, Iorio E, et al. Reactive oxygen species (ROS) and male fertility. New Discoveries in Embryology. 2015, doi: 10.5772/60632.
33. Ayaz A, Agarwal A, Sharma R, et al. Impact of precise modulation of reactive oxygen species levels on spermatozoa proteins in infertile men. Clin Proteomics. 2015; 12(1): 4, doi: 10.1186/1559-0275-12-4, indexed in Pubmed: 25972767.
34. Agarwal A, Roychoudhury S, Bjugstad KB, et al. Oxidation-reduction potential of semen: what is its role in the treatment of male infertility? Ther Adv Urol. 2016; 8(5): 302–318, doi: 10.1177/1756287216652779, indexed in Pubmed: 27695529.
35. Adewoyin M, Ibrahim M, Roszaman R, et al. Male infertility: the effect of natural antioxidants and phytocompounds on seminal oxidative stress. Diseases. 2017; 5(1): 9, doi: 10.3390/diseases5010009, indexed in Pubmed: 28933362.
36. Talevi R, Barbato V, Fiorentino I, et al. Protective effects of in vitro treatment with zinc, d-aspartate and coenzyme q10 on human sperm motility, lipid peroxidation and DNA fragmentation. Reprod Biol Endocrinol. 2013; 11: 81, doi: 10.1186/1477-7827-11-81, indexed in Pubmed: 23958080.
37. Martin-Hidalgo D, Bragado MJ, Batista AR, et al. Antioxidants and male fertility: from molecular studies to clinical evidence. Antioxidants (Basel). 2019; 8(4): 89, doi: 10.3390/antiox8040089, indexed in Pubmed: 30959797.
38. Nowicka-Bauer K, Nixon B. Molecular changes induced by oxidative stress that impair human sperm motility. Antioxidants (Basel). 2020; 9(2): 134, doi: 10.3390/antiox9020134, indexed in Pubmed: 32033035.
39. Li Y, Sun Y, Ni A, et al. Seminal plasma proteome as an indicator of sperm dysfunction and low sperm motility in chickens. Mol Cell Proteomics. 2020; 19(6): 1035–1046, doi: 10.1074/mcp.RA120.002017, indexed in Pubmed: 32312844.
40. Rizkallah N, Chambers CG, de Graaf SP, et al. Factors affecting the survival of ram spermatozoa during liquid storage and options for improvement. Animals (Basel). 2022; 12(3): 244, doi: 10.3390/ani12030244, indexed in Pubmed: 35158568.
41. Su LJ, Zhang JH, Gomez H, et al. Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis. Oxid Med Cell Longev. 2019; 2019: 5080843, doi: 10.1155/2019/5080843, indexed in Pubmed: 31737171.
42. Cito G, Becatti M, Natali A, et al. Redox status assessment in infertile patients with non-obstructive azoospermia undergoing testicular sperm extraction: A prospective study. Andrology. 2020; 8(2): 364–371, doi: 10.1111/andr.12721, indexed in Pubmed: 31654557.
43. Agarwal A, Virk G, Ong C, et al. Effect of oxidative stress on male reproduction. World J Mens Health. 2014; 32(1): 1–17, doi: 10.5534/wjmh.2014.32.1.1, indexed in Pubmed: 24872947.
44. Zribi N, Chakroun NF, Elleuch H, et al. Sperm DNA fragmentation and oxidation are independent of malondialdheyde. Reprod Biol Endocrinol. 2011; 9: 47, doi: 10.1186/1477-7827-9-47, indexed in Pubmed: 21492479.
45. Taken K, Ekin S, Arısoy A, et al. Erectile dysfunction is a marker for obstructive sleep apnea. Aging Male. 2016; 19(2): 102–105, doi: 10.3109/13685538.2015.1131259, indexed in Pubmed: 26758960.
46. Kasperczyk A, Dobrakowski M, Czuba ZP, et al. Influence of iron on sperm motility and selected oxidative stress parameters in fertile males — a pilot study. Ann Agric Environ Med. 2016; 23(2): 292–296, doi: 10.5604/12321966.1203893, indexed in Pubmed: 27294635.
47. Morales M, Munné-Bosch S. Malondialdehyde: facts and artifacts. Plant Physiol. 2019; 180(3): 1246–1250, doi: 10.1104/pp.19.00405, indexed in Pubmed: 31253746.
48. Gutiérrez-Salinas J, García-Ortíz L, González JM, et al. In vitro effect of sodium fluoride on malondialdehyde concentration and on superoxide dismutase, catalase, and glutathione peroxidase in human erythrocytes. ScientificWorldJournal. 2013; 2013: 864718, doi: 10.1155/2013/864718, indexed in Pubmed: 24223512.
49. Naher ZU, Ali M, Biswas SK, et al. Effect of oxidative stress in male infertility. Mymensingh Med J. 2013; 22(1): 136–142, indexed in Pubmed: 23416821.
50. Li Ke, Shang X, Chen Y. High-performance liquid chromatographic detection of lipid peroxidation in human seminal plasma and its application to male infertility. Clin Chim Acta. 2004; 346(2): 199–203, doi: 10.1016/j.cccn.2004.03.013, indexed in Pubmed: 15256321.
51. Fraczek M, Sanocka D, Kamieniczna M, et al. Proinflammatory cytokines as an intermediate factor enhancing lipid sperm membrane peroxidation in in vitro conditions. J Androl. 2008; 29(1): 85–92, doi: 10.2164/jandrol.107.003319, indexed in Pubmed: 17804865.
52. Ajina T, Sallem A, Haouas Z, et al. Total antioxidant status and lipid peroxidation with and without in vitro zinc supplementation in infertile men. Andrologia. 2016; 49(7): e12703, doi: 10.1111/and.12703.
53. Shamsi MB, Venkatesh S, Kumar R, et al. Antioxidant levels in blood and seminal plasma and their impact on sperm parameters in infertile men. Indian J Biochem Biophys. 2010; 47(1): 38–43, indexed in Pubmed: 21086753.
54. Benedetti S, Tagliamonte MC, Catalani S, et al. Differences in blood and semen oxidative status in fertile and infertile men, and their relationship with sperm quality. Reprod Biomed Online. 2012; 25(3): 300–306, doi: 10.1016/j.rbmo.2012.05.011, indexed in Pubmed: 22818093.
55. Gambera L, Stendardi A, Ghelardi C, et al. Effects of antioxidant treatment on seminal parameters in patients undergoing in vitro fertilization. Arch Ital Urol Androl. 2019; 91(3), doi: 10.4081/aiua.2019.3.187, indexed in Pubmed: 31577104.
56. Alahmar AT, Calogero AE, Singh R, et al. Coenzyme Q10, oxidative stress, and male infertility: A review. Clin Exp Reprod Med. 2021; 48(2): 97–104, doi: 10.5653/cerm.2020.04175, indexed in Pubmed: 34078005.
57. Wadhwa L, Priyadarshini S, Fauzdar A, et al. Impact of vitamin D supplementation on semen quality in vitamin d-deficient infertile males with oligoasthenozoospermia. J Obstet Gynaecol India. 2020; 70(1): 44–49, doi: 10.1007/s13224-019-01251-1, indexed in Pubmed: 32030005.

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2024, vol. 95, no. 6, 434–442

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/gpl.95791

Evaluation of the risk of thyroid cancer following hysterectomy through meta-analysis

Ozkan Balcin[1, 2], Ilker Ercan[3], Arda Uzunoglu[2]

[1]*Bursa City Hospital, Department of General Surgery, Dogankoy, Bursa, Türkiye*
[2]*Bursa Uludag University, Institute of Health Sciences, Department of Biostatistics, Gorukle, Bursa, Türkiye*
[3]*Department of Biostatistics, Uludag University, Faculty of Medicine, Bursa, Türkiye*

ABSTRACT

Objectives: Thyroid cancer is observed more frequently in women than men, possibly due to the influence of hormonal factors. This study aims to conduct a meta-analysis encompassing both prospective and retrospective observational studies to examine the risk of thyroid cancer in women who have undergone hysterectomy surgery.

Material and methods: The literature search identified 356 articles by May 2022, and eight reported hazard ratios for thyroid cancer in women who underwent hysterectomy surgery. After the eliminations, we performed three different meta-analyses with studies that included patients who underwent only total abdominal hysterectomy (TAH), total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO), and underwent hysterectomy with or without BSO. The reporting of this study has been conducted in accordance with the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews).

Results: Our study showcases a comprehensive meta-analysis that includes eight observational studies, both retrospective and prospective, exploring the link between hysterectomy and the likelihood of developing thyroid cancer. This analysis is based on data from more than 12 million individuals, encompassing over 24,000 cases. Women who had undergone TAH (HR = 1.586, 95% CI: 1.382–1.819, $p < 0.001$), women who had undergone TAH and BSO (HR = 1.420, 95% CI: 1.205–1.675, $p < 0.001$), and women who had undergone hysterectomy with or without BSO had an increased risk (HR = 1.623, 95% CI: 1.387–1.899, $p < 0.001$) of developing thyroid cancer later in life.

Conclusions: We found that hysterectomy had a statistically significant risk effect on the development of thyroid cancer. The limited number of previous studies, the low amount of information, the lack of homogeneous distribution of the patients in the studies, and the unknown characteristics of thyroid cancer developing after hysterectomy were the limitations of this study. Nevertheless, our findings can positively affect public health because of the potential to enlighten the etiological mechanisms leading to thyroid cancer. Future researches should first aim to explain the underlying mechanisms of developing thyroid cancer after hysterectomy.

Keywords: thyroid cancer; hysterectomy; oophorectomy; artificial menopause; surgical menopause; meta-analysis

Ginekologia Polska 2024; 95, 6: 434–442

INTRODUCTION

Among the malignancies affecting the endocrine system, thyroid cancer is the most prevalent [1–2]. Over the decades, there has been a global increase in the incidence of thyroid cancer [3–4]. Ionizing radiation, benign diseases of the thyroid, a genetic inclination, and elevated body mass index are among the recognized risk factors for thyroid cancer [3, 5, 6]. Based on epidemiological studies, it is possible to say that hormonal factors can create or regulate the risk of thyroid cancer. Indeed, the occurrence of thyroid cancer is three times higher in women compared to men [7–9]. This rate against women is at its highest point in reproductive age, and it gradually decreases as the age progresses [9]. Therefore, this suggests that reproductive factors and sex hormones may cause a higher incidence in women. It has been proposed that estrogen plays a role in the etiology of thyroid cancer by directly affecting proliferative and neoplastic pathways through receptors [10]. In addition, the fact that women use health services more in reproductive age than men [11] increases the likelihood

Corresponding author:
Ozkan Balcin
Bursa City Hospital, Department of General Surgery, Dogankoy, 16110 Bursa, Türkiye
e-mail: dr.balcin@hotmail.com

Received: 30.05.2023 Accepted: 28.08.2023 Early publication date: 15.01.2024

of incidental and may constitute a gender difference in incidence. Although several studies have investigated the relationship between reproductive exposures and thyroid cancer risk (*e.g.*, pregnancy, breastfeeding, menarche/menopausal age, and oral contraceptive use), no clear association has been shown for most [12–14].

Both *in vitro* and *in vivo* research have demonstrated the ability of estrogen to promote the growth and modulate the metastatic characteristics of human thyroid tumor cells [15–18]. The estrogen receptor (ER) provides the estrogen effect primarily [10]. As evidenced by increased proliferation and ERs expression, estrogen increases cell adhesion, migration, and invasion, which means that both benign and malignant thyroid cells respond to estrogen [16]. Moreover, there is evidence that estrogen acts by inducing the growth of human thyroid tumor cells through the mitogen-activated protein kinase pathway [15]. Different epidemiological research exploring the link between the predominance of females and reproductive and hormonal factors in thyroid cancer have not been able to identify robust or consistent correlations [19–20].

Hysterectomy, whether performed with or without bilateral salpingo-oophorectomy (BSO), is one of the most common gynecological surgeries among women [21]. The BSO procedure leads to surgical menopause in women who have not yet experienced natural menopause [22]. This surgical menopause results in a sudden decrease in estrogen levels [22]. Moreover, hysterectomy without BSO can also impair ovarian function by disrupting the blood flow to the ovaries or causing damage to ovarian tissue [23–24]. Therefore, premenopausal women experience menopause earlier after hysterectomy than those who do not have hysterectomy [25]. In this regard, various epidemiological studies have been conducted, assuming the development of thyroid cancer after hysterectomy, after hysterectomy and BSO, and after hysterectomy with or without BSO. Various cohort-type studies have examined the relationship between hysterectomy and the subsequent risk of developing thyroid cancer. However, studies on this subject are limited in number. In some of the studies conducted, an association was found between hysterectomy and the risk of thyroid cancer. However, this association has not been shown in some of them. The relationship between external estrogen exposure as a potential risk factor for thyroid cancer, and the early depletion of natural estrogen as a possible protective factor against it, remains intricate and yet to be fully understood. All this suggests that higher evidentiary scientific data are needed to clarify its success in predicting the risk of thyroid cancer after hysterectomy. Consequently, the primary goal of this meta-analysis was to elucidate the correlation between undergoing a hysterectomy and the associated risk of developing thyroid cancer.

MATERIAL AND METHODS

Search strategy

Using a systematic electronic search approach as of May 2022, we conducted a search for published literature in various databases including PubMed, Medline, Google Scholar, Scopus, Web of Science, and Science Direct. The data of our study were deciphered from all the studies conducted. The following keywords and combinations were used: thyroid cancer, hysterectomy, oophorectomy, artificial menopause, surgical menopause, and meta-analysis. The search was limited to being published in English and conducted on people. The search strategy schematically presents the decode flow diagram (Fig. 1). Our research adheres to the standards set by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) guidelines, as outlined in reference [26–27].

Inclusion criteria

The inclusion criteria were as follows:

1. Estimating the association between types of hysterectomy and thyroid cancer risk in women.
2. Cohort or case-control design.
3. Showing hazard ratios (HRs) with 95 % confidence intervals [95 % confidence intervals (CIs)].

Case-only studies and studies not about the relationship of types of hysterectomy with the risk of thyroid cancer were all excluded.

Study selection

We acquired the full texts of all articles that were potentially suitable for this meta-analysis, based on their abstracts. Additionally, we conducted a search for extra articles in the reference lists of the retrieved articles as well as in previously published reviews and meta-analyses. In addition to all observational studies investigating the relationship between hysterectomy and the development of thyroid cancer, retrospective or prospective studies were selected. Studies that developed thyroid cancer after hysterectomy, after hysterectomy and BSO, and after hysterectomy with or without BSO were included in this meta-analysis. No specific year interval was determined for the development of thyroid cancer, and the specified intervals were not considered. Studies in which subgroup thyroid cancers were investigated, except for thyroid cancer in general and patients who underwent BSO alone without hysterectomy, were excluded. Case reports were excluded from this analysis. Additionally, trials that presented results in a manner that obstructed data collection, such as not reporting statistical information, were also excluded. Finally, after the eliminations, we conducted three different meta-analyses with studies that only included patients who underwent TAH, TAH and BSO, and

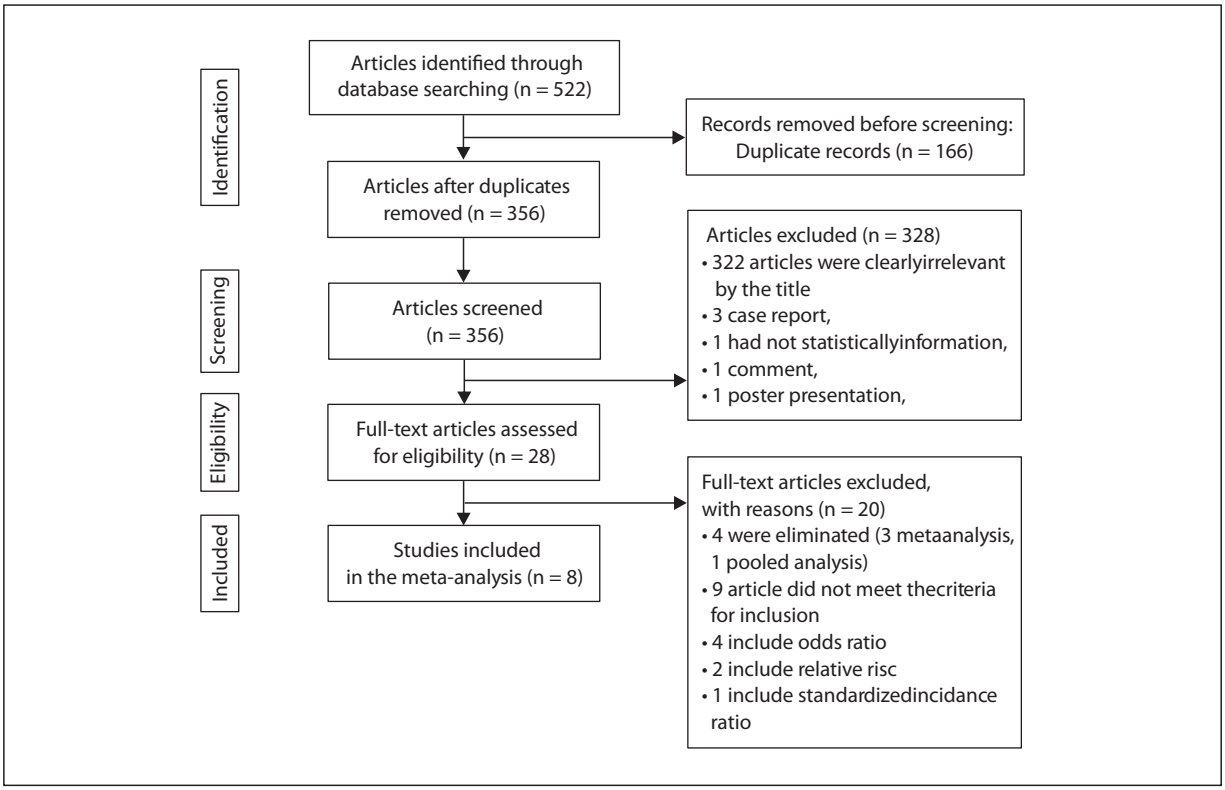


Figure 1. Flow chart

underwent hysterectomy with or without BSO. The articles included in the meta-analysis were those that provided or allowed the estimation of the hazard ratio for the association between hysterectomy and the risk of thyroid cancer among women. These articles also included 95% confidence intervals, standard errors, or variance. No language, time, or geographical restrictions were applied. There was no direct funding for this research.

Quality and risk of bias assessment

Prior to the meta-analysis, the publication bias of the studies was assessed using Begg's and Egger's tests.

Data extraction

The studies were selected through a three-stage process. Initially, the titles and abstracts of all electronic articles were evaluated for eligibility. Subsequently, the decision to include certain studies in this meta-analysis was made after obtaining and reviewing the full texts of articles deemed potentially suitable. Any potential discrepancies in this final stage were resolved through the consensus of all authors.

Summary measures

The primary outcome measure selected for this meta-analysis was to determine whether the risk of thyroid cancer following hysterectomy was significant.

Quantitative data synthesis

In our study, we conducted a meta-analysis using hazard ratios. In some studies included in the meta-analysis, estimates of the hazard ratios were provided, but the variance information was neglected. If there is a $(1 - x_i) \times 100$ percent confidence interval specified, this provides a method for calculating the variance of the logarithmic hazard ratio. In this context, $UPPCI_i$ and $LOWCI_i$ are the values representing the lower and upper limits of the confidence interval for $\ln(HR_i)$ that is, for the logarithmic hazard ratio. Typically, confidence intervals specified for hazard ratios are more common. In this case, $UPPCI_i$ and $LOWCI_i$ are expressed as the logarithms of the upper and lower limits of the hazard ratio [28].

Standard errors were estimated with the formula:

$$\mathrm{var}(\ln(HR_i)) = \left[\frac{UPP\ CI_i - LOW\ CI_i}{2\Phi^{-1}(1-\alpha_i/2)}\right]^2$$

$UPP\ CI_i$ — the value for the upper ends of the confidence interval [28]

$LOW\ CI_i$ — the value for the lower ends of the confidence interval [28]

$2\Phi^{-1}(1-\alpha_i/2)$ — We note that in practice the 95 percent intervals are usually given, and thus the denominator inside

the square brackets in expression will usually take the value of 2 × 1.96 [28]

Suppose that there are k trials, and for each trial, i = 1.2, k [28]

When determining the statistical methods, the heterogeneity of the studies was assessed using the Cochran Q test. For the homogeneity and publication bias tests of the studies, the value of α was set at 0.10.

The I^2 index is a more recent approach to quantify heterogeneity in meta-analyses. I^2 provides an estimate of the percentage of variability in results across studies that is due to real differences and not due to chance. The I^2 index measures the extent of heterogeneity by dividing the result of Cochran's Q test and its degrees of freedom by the Q-value itself [29].

When heterogeneity was identified in the studies through Cochran's Q test, the DerSimonian-Laird methodology, based on the random-effects model, was chosen for the analyses. For the statistical evaluations, version 19 of the MedCalc software was employed.

RESULTS

Literature search and study characteristics

Search of the literature yielded 356 articles (refer to Fig. 1). Out of these, 322 were deemed unrelated based on their titles. Among the remaining, three were case reports, with one lacking statistical data [30], another being a commentary, and one more a poster presentation. The full texts of the remaining 28 articles were thoroughly evaluated.

Upon evaluating the full texts of 28 articles, four were omitted from the study. This exclusion included three articles because they were meta-analyses and one due to it being a pooled analysis. Specifically, one of the meta-analyses investigated the relationship between the use of external sex hormones in women and the risk of developing thyroid cancer [31]. The others are about hormonal and reproductive factors in women and thyroid cancer risk [32–33]. So lastly, one pooled analysis of case-control of thyroid cancer [34]. When the full texts were examined, it was seen that nine articles did not meet the inclusion criteria in terms of hysterectomy types. However, when the remaining 15 articles were divided into groups, eight articles [19, 35–41] indicated the hazard ratio for thyroid cancer, four articles the odds ratio, two articles the relative risk, and 1 article the standardized incidence ratio. Thus, eight articles remained to be included in the meta-analysis [19, 35–41]. Table 1 presents the pertinent attributes of the trials that were included.

The meta-analysis incorporated eight articles, published from 2012 through 2021, with study populations varying from 70,047 to 5,491,438 individuals. These studies provided hazard ratios assessing the likelihood of developing thyroid cancer following different types of hysterectomy. Analytical subgroups were categorized into three main sections: Firstly, assessing the risk in women who had TAH only; secondly, those who had both TAH and BSO; and lastly, women who had a hysterectomy, either with or without BSO, evaluating all cases through their respective hazard ratios. Four articles [19, 35–37] for thyroid cancer after TAH, seven articles [19, 35–37, 39–41] for thyroid cancer after

Table 1. Characteristics of all studies included in our meta-analysis

Authors	Study type/country	Total No. of people included in the study (n)	TAH (n)	TAH and BSO (n)	Hysterectomy ± ± USO/BSO (n)	Total no. of patients with thyroid Ca (n)
Wilson 2021 [35]	Retrospective-Cohort Australia	838,237	74.056	25.920		1.095
Kim 2021 [36]	Retrospective-Cohort Korea	671,291	42.848	36.113		12.959
Guenego 2018 [37]	Prospective-Cohort France	89.340	7.263	8.918	16,064	412
Falconer 2017 [38]	Retrospective-Cohort Sweden	5,470,078			90,235	2.935
Altman 2016 [39]	Retrospective-Cohort Sweden	5,491,438	90.235	21.360	111,595	6.869
Luo 2016 [19]	Prospective-Cohort USA, China	127,566	10.675	13.880	46,852	344
Braganza 2015 [41]	Prospective-Cohort France	70.047				48
Kabat 2012 [40]	Prospective-Cohort USA	145,007				296
Total		12,903,004				24.958

BSO — bilateral salpingo-oophorectomy; TAH — total abdominal hysterectomy; USO — unilateral salpingo-oophorectomy

Table 2. Relevant statistics for meta-analysis in determining the association between total abdominal hysterectomy (TAH) and malign thyroid neoplasm in trials

Study	Ln (HR)	Standard error	HR	95% CI	z	p value	Weight [%]	
							Fixed	Random
Wilson et al., 2021	0.322	0.0755	1.380	1.190 to 1.600			14.02	29.57
Kim et al., 2021	0.519	0.0318	1.680	1.578 to 1.788			78.93	41.22
Guenego et al., 2018	0.673	0.152	1.960	1.455 to 2.641			3.46	14.43
Luo et al., 2016	0.372	0.149	1.450	1.082 to 1.943			3.58	14.78
Total (random effects)	0.461	0.0701	1.586	1.382 to 1.819	6.580	< 0.001	100.00	100.00

HR — hazard ratio; CI — confidence interval

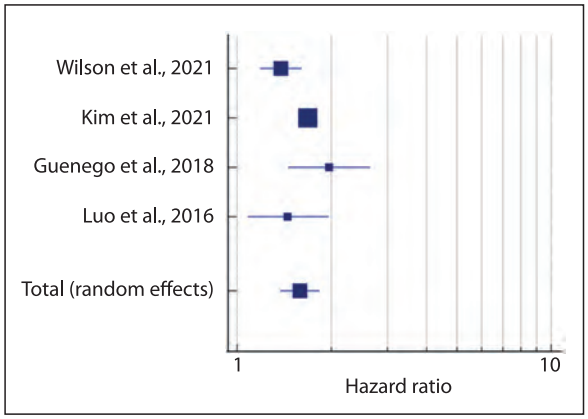


Figure 2. Forest graph in evaluating the association between total abdominal hysterectomy (TAH) and thyroid malignant neoplasm

TAH and BSO, and six articles [19, 37–41] for thyroid cancer after hysterectomy with or without BSO were included in the meta-analysis.

Qualitative analysis

Except for three, all studies reported a relation between hysterectomy and the risk of developing thyroid cancer afterward.

Quantitative analysis

In the initial meta-analysis, publication bias was assessed using Egger's test (p = 0.694) and Begg's test (p = 1.000), both indicating its absence. Cochran's Q-test indicated significant heterogeneity (p = 0.049, I^2 = 61.71%). A notable disparity was observed between the patient group and the control group. The risk of developing thyroid cancer later in life was higher in women who TAH, as shown by the hazard ratio (HR = 1.586, 95% CI: 1.382–1.819, p < 0.001) (refer to Tab. 2). Figure 2 illustrates these meta-analysis findings.

The subsequent meta-analysis revealed no publication bias, as demonstrated by Egger's test (p = 0.912) and Begg's test (p = 0.880). Cochran's Q-test showed heterogeneity in the data (p = 0.012, I^2 = 63.23%). A significant variation was found between the patient and control groups. The analysis indicated that women who underwent TAH along with BSO were at a heightened risk (HR = 1.420, 95% CI: 1.205–1.675, p < 0.001) of developing thyroid cancer later (detailed in Tab. 3). Figure 3 displays these results.

In the third meta-analysis, the Egger's test (p = 0.195) and the Begg's test (p = 0.107) ruled out the presence of publication bias. Heterogeneity was confirmed by Cochran's Q-test (p = 0.025, I^2 = 61.05%). There was a marked difference between the control group and patients. Increased risk of thyroid cancer in later life was noted in women who had undergone a hysterectomy, with or without BSO (HR = 1.623, 95% CI: 1.387–1.899, p < 0.001), as detailed in Table 4. The outcomes are depicted in Figure 4.

DISCUSSION

Our meta-analysis, which examined both retrospective and prospective observational studies, investigated the link between hysterectomy and the risk of thyroid cancer. This analysis encompassed over 24,000 cases within a population exceeding 12 million. The findings indicated a statistically significant association between hysterectomy and an increased risk of developing thyroid cancer.

Many studies in the literature investigate the relationship between hormonal and reproductive factors and the risk of thyroid cancer and find conflicting evidence. Hormonal and reproductive factors have been implicated in the development of thyroid cancer, but the molecular mechanisms explaining the exact association have not yet been fully comprehended. Although men have a constant increase in the risk of thyroid cancer throughout their lives, the risk increases in women during puberty and decreases after menopause [42], supporting the idea that hormonal factors are influential in thyroid cancer. It is estimated that estrogen increases the level of TSH and, as a result, causes the growth of thyroid cells [42]. Also, estrogen receptors are highly expressed in thyroid tumor cells [42]. Thyroid carcinogenesis can be influenced by sex steroid hormones,

Table 3. Relevant statistics for meta-analysis in determining the association between Total abdominal Hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO) and thyroid malignant neoplasm in trials

Study	Ln (HR)	Standard error	HR	95% CI	z	p value	Weight [%]	
							Fixed	Random
Wilson et al., 2021	0.166	0.137	1.180	0.902 to 1.544			5.95	15.54
Kim et al., 2021	0.322	0.0388	1.380	1.279 to 1.489			74.40	25.09
Guenego et al., 2018	0.854	0.144	2.350	1.773 to 3.115			5.40	14.92
Altman et al., 2016	0.104	0.267	1.110	0.658 to 1.873			1.57	7.20
Luo et al, 2016	0.392	0.137	1.480	1.132 to 1.934			5.99	15.59
Braganza et al., 2015	0.191	0.272	1.210	0.710 to 2.061			1.51	7.02
Kabat et al., 2012	0.239	0.147	1.270	0.952 to 1.694			5.17	14.63
Total (random effects)	0.351	0.0840	1.420	1.205 to 1.675	4.179	< 0.001	100.00	100.00

HR — hazard ratio; CI — confidence interval

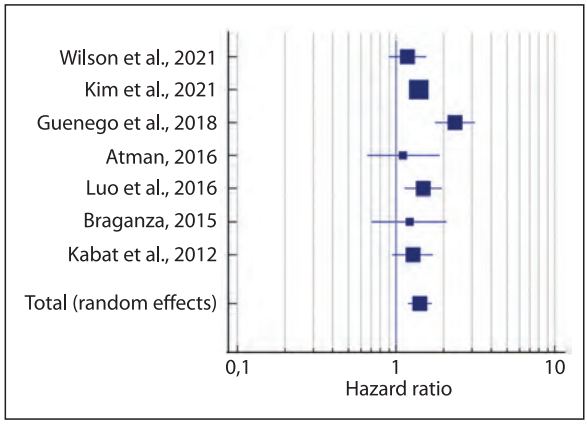


Figure 3. Forest graph in evaluating the association between total abdominal hysterectomy (TAH) + bilateral salpingo-oophorectomy (BSO) and thyroid malignant neoplasm

which promote thyroid cell proliferation and interact with immune functions. In vitro studies have shown that estradiol enhances metastatic properties such as adhesion, migration, and invasiveness in thyroid cells, thereby facilitating the growth of thyroid tumor cells [16]. Research indicates the presence of progesterone receptors on both normal and cancerous thyroid cells [43], as well as on certain immune system cells [44]. Given the known effect of progesterone in stimulating the growth of uterine fibroids [45], it might also play a crucial role in the initiation and development of thyroid cancers. If BSO has also been performed on women who have had a hysterectomy, hormone replacement therapy will be prescribed. In this regard, we can believe that estrogen and progesterone or only estrogen will stimulate the development of thyroid cancer.

Conversely, the study by Braganza and colleagues found no correlation between menopausal hormone therapy in women, regardless of their hysterectomy history, and thyroid cancer risk [41]. This prospective research highlighted that factors such as a greater number of reproductive years, more frequent ovulation cycles, and the presence of uterine fibroids — all indicative of prolonged exposure to endogenous hormones — were associated with a heightened risk of thyroid cancer [41]. Luo et al. [19], in their study, observed that hysterectomy with or without oophorectomy was linked to an increased risk of thyroid cancer in postmenopausal women. Nevertheless, their findings did not corroborate the theories suggesting that external sources of estrogen increase thyroid cancer risk or that the lack of estrogen acts as a protective agent against this cancer [19]. In addition, Kim et al. [36] similarly did not support this hypothesis in the national cohort of the Korean general population. On the other hand, should elevated estrogen levels be a contributing factor to thyroid cancer, one might anticipate a reduced risk of this cancer in cases of hysterectomy, particularly when accompanied by BSO, due to the abrupt decrease in estrogen levels following BSO. One study showed that women who underwent hysterectomy and did not have an oophorectomy had no increased risk of thyroid cancer, but women with BSO had an increased risk of the disease [20]. It is evident that the hypothesis suggesting external estrogen as a risk factor for thyroid cancers or the absence of estrogen as a protective agent is weak and insufficient.

Several studies have reported that hysterectomy increases the risk of thyroid cancer [20, 46–48], but not all studies have observed this [40, 49–50]. Another study that has confused the literature on the subject is the retrospective cohort of Sweden [39]. Altmann et al. [39] found that the risk of thyroid cancer increases only in women who underwent a hysterectomy. However, the addition of BSO to the operation did not lead to an additional increase in the risk of thyroid cancer. Studies often categorize artificial menopause as resulting from surgical procedures like hysterectomy and/or bilateral oophorectomy, which have been previously linked to a heightened risk of thyroid cancer [13,

Table 4. Relevant statistics for meta-analysis in determining the association between hysterectomy with or without bilateral salpingo-oophorectomy (BSO) and thyroid malignant neoplasm in trials

Study	Ln (HR)	Standard error	HR	95% CI	z	p value	Weight [%]	
							Fixed	Random
Guenego et al., 2018	0.765	0.114	2.150	1.719 to 2.689			17.95	17.98
Falconer et al., 2017	0.565	0.0993	1.760	1.449 to 2.138			23.70	19.73
Altman et al., 2016	0.565	0.0993	1.760	1.449 to 2.138			23.70	19.73
Luo et al., 2016	0.378	0.119	1.460	1.156 to 1.844			16.48	17.41
Braganza et al., 2015	0.199	0.215	1.220	0.800 to 1.860			5.04	9.30
Kabat et al., 2012	0.247	0.133	1.280	0.986 to 1.662			13.13	15.86
Total (random effects)	0.484	0.0801	1.623	1.387 to 1.899	6.046	< 0.001	100.00	100.00

HR — hazard ratio; CI — confidence interval

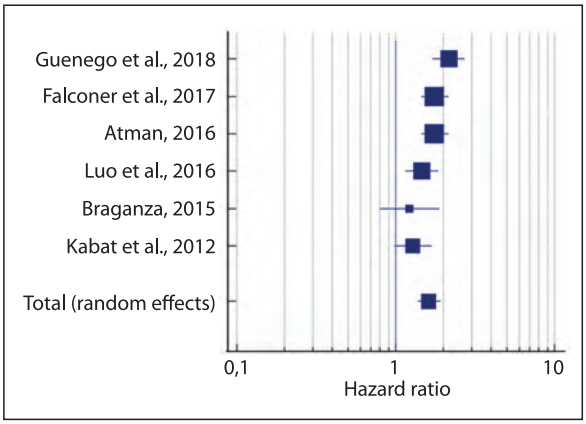


Figure 4. Forest graph in evaluating the association between hysterectomy with or without bilateral salpingo-oophorectomy (BSO) and thyroid malignant neoplasm in trials

34, 50]. In contrast, research by Guonego and colleagues [37] indicated that a history of oophorectomy, especially when combined with hysterectomy, did not correlate with an increased risk of thyroid cancer, nor did it significantly alter the relationship between hysterectomy and thyroid cancer risk. These findings align with those from the WHI cohort, where Kabat and team reported no significant link between the risk of thyroid cancer and bilateral oophorectomy.

Although thyroid cancer occurs more frequently in women compared to men, the specific endocrine reasons behind this disparity are yet to be completely understood. Hormone replacement therapy is not given to premenopausal patients unless bilateral oophorectomy is performed in addition to hysterectomy. Therefore, hormone replacement therapy after hysterectomy cannot clearly explain the increased risk of thyroid cancer in women with only a hysterectomy. Dysfunctional menstrual bleeding, one of the most common indications for hysterectomy worldwide, is often associated with thyroid dysfunction [51]. All types of benign thyroid lesions increase the risk of thyroid cancer, and hypothyroidism can also be found in both menopause and metrorrhagia. In this case, hysterectomy may be an intermediary for thyroid cancer that develops due to menstrual disorders, not the cause of thyroid cancer. Research in humans and animals has revealed that uterine factors influence the formation and release of various non-steroidal substances, including neurokinin, substance P, and vasoactive peptides. These factors also play a significant role in the growth of endocrine organs such as the adrenal and thyroid glands [52–53]. In this context, it is considered that hysterectomy may directly affect the thyroid gland, contributing to the carcinogenic transformation of thyroid epithelial or parafollicular cells. However, as previously discussed, there might be a connection between menstrual-related disorders and benign thyroid conditions through the hypothalamic-pituitary-thyroid axis (HPT axis), suggesting that in these cases, hysterectomy might act more as an intermediary factor rather than a direct cause. By this logic, hysterectomy itself has no biological relationship with thyroid cancer risk. Instead, it is a consequence of thyroid dysfunction that manifests in bleeding disorders and eventually results in hysterectomy. The association between a history of hysterectomy and an increased risk of thyroid cancer may be partly due to the common co-occurrence of uterine leiomyomas (a primary reason for hysterectomy) with thyroid nodules [54]. The relationship between hysterectomy and thyroid cancer may also be due to more case detection, as women with dysfunctional uterine bleeding may be greater likely to have thyroid dysfunction leading to ongoing monitoring and further investigative procedures [37].

This meta-analysis has been conducted under several limitations. One of the limitations is that the meta-analysis has not been separated by hormone replacement therapy usage because of the scarce number of previous studies and a very limited amount of information shared in the studies. In addition to this first limitation, it is believed that the distribution of patients in the studies is not homogeneous. We

think heterogeneity may be caused by many reasons, such as differences in surgical procedures or postoperative hormone replacement therapies in the studies, different quality levels, and other methods used to measure the results. Heterogeneity may be due to a known reason, such as that some of the women included in the studies were premenopausal and some were postmenopausal, or it may be due to an unexplained reason. There is a high probability that the hysterectomy performed in premenopausal women and the hysterectomy performed in postmenopausal women are likely to have different risk levels of thyroid cancer. In addition, the studies do not clarify gravida and parity numbers and lactation history, in which estrogen and progesterone balance changes. The presence of familial syndromes with increased risk of thyroid cancer, whether the patients were exposed to radiation in any period of their lives, whether the patients had thyroid nodules in their preoperative lives, and the history of anti-thyroid drug use similarly disrupt the homogeneity of the studies. Thirdly, tumor sizes, invasion of non-thyroid tissues, and metastases to lymph nodes are not known in thyroid cancers developing after hysterectomy. Nevertheless, it is believed that our results deserve careful attention regarding the fact that the findings can have positive effects on public health because of the potential to enlighten the etiological mechanisms leading to thyroid cancer. Within this context, future researches should first aim to explain the underlying mechanisms of developing thyroid cancer after hysterectomy.

Article information and declarations

Author contributions

All authors contributed to the study's conception and design, commented on previous versions of the manuscript, and at the end, read and approved the final manuscript.
Ozkan Balcin — conceptualization, methodology, resources, data curation, writing — original draft, visualization; Ilker Ercan — validation, writing — review and editing, supervision; Arda Uzunoglu — formal analysis, resources.
Each author contributed significantly to the development and design, data analysis and interpretation, and drafting or critical revision of the article for key intellectual content. They also approved the final manuscript. This manuscript is unique to this submission and is not currently under consideration by any other journal or publishing entity. Furthermore, the authors declare no financial interest or affiliation with any organization that could be perceived as influencing the subject matter of this manuscript.

Acknowledgments

I am grateful to all of those with whom I have had the pleasure to work during this and other related projects. Each of the authors has provided me extensive personal and professional guidance and taught me a great deal about scientific research.

Funding

No specific grants were received from any public, commercial, or not-for-profit funding agencies for this research.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Fitzmaurice C, Dicker D, Pain A, et al. Global Burden of Disease Cancer Collaboration. The global burden of cancer 2013. JAMA Oncol. 2015; 1(4): 505–527, doi: 10.1001/jamaoncol.2015.0735, indexed in Pubmed: 26181261.
2. Lubitz CC, Kong CY, McMahon PM, et al. Annual financial impact of well-differentiated thyroid cancer care in the United States. Cancer. 2014; 120(9): 1345–1352, doi: 10.1002/cncr.28562, indexed in Pubmed: 24481684.
3. Schneider DF, Chen H. New developments in the diagnosis and treatment of thyroid cancer. CA Cancer J Clin. 2013; 63(6): 374–394, doi: 10.3322/caac.21195, indexed in Pubmed: 23797834.
4. Colonna M, Uhry Z, Guizard AV, et al. FRANCIM network. Recent trends in incidence, geographical distribution, and survival of papillary thyroid cancer in France. Cancer Epidemiol. 2015; 39(4): 511–518, doi: 10.1016/j.canep.2015.04.015, indexed in Pubmed: 26003877.
5. Clavel-Chapelon F, Guillas G, Tondeur L, et al. Risk of differentiated thyroid cancer in relation to adult weight, height and body shape over life: the French E3N cohort. Int J Cancer. 2010; 126(12): 2984–2990, doi: 10.1002/ijc.25066, indexed in Pubmed: 19950225.
6. Trésallet C, Seman M, Tissier F, et al. The incidence of papillary thyroid carcinoma and outcomes in operative patients according to their body mass indices. Surgery. 2014; 156(5): 1145–1152, doi: 10.1016/j.surg.2014.04.020, indexed in Pubmed: 24878452.
7. Rahbari R, Zhang L, Kebebew E. Thyroid cancer gender disparity. Future Oncol. 2010; 6(11): 1771–1779, doi: 10.2217/fon.10.127, indexed in Pubmed: 21142662.
8. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5): E359–E386, doi: 10.1002/ijc.29210, indexed in Pubmed: 25220842.
9. Moleti M, Sturniolo G, Di Mauro M, et al. Female Reproductive Factors and Differentiated Thyroid Cancer. Front Endocrinol (Lausanne). 2017; 8: 111, doi: 10.3389/fendo.2017.00111, indexed in Pubmed: 28588554.
10. Derwahl M, Nicula D. Estrogen and its role in thyroid cancer. Endocr Relat Cancer. 2014; 21(5): T273–T283, doi: 10.1530/ERC-14-0053, indexed in Pubmed: 25052473.
11. Bayram C, Valenti L, Britt H. General practice encounters with men. Aust Fam Physician. 2016; 45(4): 171–174, indexed in Pubmed: 27052128.
12. Cordina-Duverger E, Leux C, Neri M, et al. Hormonal and reproductive risk factors of papillary thyroid cancer: A population-based case-control study in France. Cancer Epidemiol. 2017; 48: 78–84, doi: 10.1016/j.canep.2017.04.001, indexed in Pubmed: 28426980.
13. Zamora-Ros R, Rinaldi S, Biessy C, et al. Reproductive and menstrual factors and risk of differentiated thyroid carcinoma: the EPIC study. Int J Cancer. 2015; 136(5): 1218–1227, doi: 10.1002/ijc.29067, indexed in Pubmed: 25041790.
14. Xhaard C, Rubino C, Cléro E, et al. Menstrual and reproductive factors in the risk of differentiated thyroid carcinoma in young women in France: a population-based case-control study. Am J Epidemiol. 2014; 180(10): 1007–1017, doi: 10.1093/aje/kwu220, indexed in Pubmed: 25269571.
15. Manole D, Schildknecht B, Gosnell B, et al. Estrogen promotes growth of human thyroid tumor cells by different molecular mechanisms. J Clin Endocrinol Metab. 2001; 86(3): 1072–1077, doi: 10.1210/jcem.86.3.7283, indexed in Pubmed: 11238488.
16. Rajoria S, Suriano R, Shanmugam A, et al. Metastatic phenotype is regulated by estrogen in thyroid cells. Thyroid. 2010; 20(1): 33–41, doi: 10.1089/thy.2009.0296, indexed in Pubmed: 20067378.

17. Xu S, Chen G, Peng W, et al. Oestrogen action on thyroid progenitor cells: relevant for the pathogenesis of thyroid nodules? J Endocrinol. 2013; 218(1): 125–133, doi: 10.1530/JOE-13-0029, indexed in Pubmed: 23645248.
18. Zane M, Parello C, Pennelli G, et al. Estrogen and thyroid cancer is a stem affair: A preliminary study. Biomed Pharmacother. 2017; 85: 399–411, doi: 10.1016/j.biopha.2016.11.043, indexed in Pubmed: 27899250.
19. Luo J, Hendryx M, Manson JE, et al. Hysterectomy, oophorectomy, and risk of thyroid cancer. J Clin Endocrinol Metab. 2016; 101(10): 3812–3819, doi: 10.1210/jc.2016-2011, indexed in Pubmed: 27459531.
20. Mack WJ, Preston-Martin S, Bernstein L, et al. Reproductive and hormonal risk factors for thyroid cancer in Los Angeles County females. Cancer Epidemiol Biomarkers Prev. 1999; 8(11): 991–997, indexed in Pubmed: 10566554.
21. Wu JM, Wechter ME, Geller EJ, et al. Hysterectomy rates in the United States, 2003. Obstet Gynecol. 2007; 110(5): 1091–1095, doi: 10.1097/01.AOG.0000285997.38553.4b, indexed in Pubmed: 17978124.
22. Tamhane N, Imudia AN, Mikhail E. Contemporary management of adnexa at the time of benign hysterectomy: a review of the literature. J Obstet Gynaecol. 2019; 39(7): 896–902, doi: 10.1080/01443615.2019.1581747, indexed in Pubmed: 31303119.
23. Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, et al. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. J Clin Endocrinol Metab. 2000; 85(2): 645–651, doi: 10.1210/jcem.85.2.6405, indexed in Pubmed: 10690870.
24. Xiangying Hu, Lili H, Yifu S. The effect of hysterectomy on ovarian blood supply and endocrine function. Climacteric. 2006; 9(4): 283–289, doi: 10.1080/13697130600865774, indexed in Pubmed: 16857658.
25. Farquhar CM, Sadler L, Harvey SA, et al. The association of hysterectomy and menopause: a prospective cohort study. BJOG. 2005; 112(7): 956–962, doi: 10.1111/j.1471-0528.2005.00696.x, indexed in Pubmed: 15957999.
26. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021; 372: n160, doi: 10.1136/bmj.n160, indexed in Pubmed: 33781993.
27. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017; 358: j4008, doi: 10.1136/bmj.j4008, indexed in Pubmed: 28935701.
28. Parmar M, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statistics in Medicine. 1998; 17(24): 2815–2834, doi: 10.1002/(sici)1097-0258(19981230)17:24<2815::aid-sim110>3.0.co;2-8, indexed in Pubmed: 9921604.
29. Hoaglin DC. Misunderstandings about Q and ‚Cochran's Q test' in meta-analysis. Stat Med. 2016; 35(4): 485–495, doi: 10.1002/sim.6632, indexed in Pubmed: 26303773.
30. Frentzel-Beyme R, Helmert U. Association between malignant tumors of the thyroid gland and exposure to environmental protective and risk factors. Rev Environ Health. 2000; 15(3): 337–358, doi: 10.1515/reveh.2000.15.3.337, indexed in Pubmed: 11048335.
31. Caini S, Gibelli B, Palli D, et al. Menstrual and reproductive history and use of exogenous sex hormones and risk of thyroid cancer among women: a meta-analysis of prospective studies. Cancer Causes Control. 2015; 26(4): 511–518, doi: 10.1007/s10552-015-0546-z, indexed in Pubmed: 25754110.
32. Mannathazhathu AS, George PS, Sudhakaran S, et al. Reproductive factors and thyroid cancer risk: meta-analysis. Head Neck. 2019; 41(12): 4199–4208, doi: 10.1002/hed.25945, indexed in Pubmed: 31595581.
33. Wang P, Lv L, Qi F, et al. Increased risk of papillary thyroid cancer related to hormonal factors in women. Tumour Biol. 2015; 36(7): 5127–5132, doi: 10.1007/s13277-015-3165-0, indexed in Pubmed: 25669169.
34. Negri E, Dal Maso L, Ron E, et al. A pooled analysis of case-control studies of thyroid cancer. II. Menstrual and reproductive factors. Cancer Causes Control. 1999; 10(2): 143–155, doi: 10.1023/a:1008880429862, indexed in Pubmed: 10231163.
35. Wilson LF, Tuesley KM, Webb PM, et al. Hysterectomy and risk of breast, colorectal, thyroid, and kidney cancer - an Australian data linkage study. Cancer Epidemiol Biomarkers Prev. 2021; 30(5): 904–911, doi: 10.1158/1055-9965.EPI-20-1670, indexed in Pubmed: 33619026.
36. Kim M, Kim BoH, Lee H, et al. Thyroid cancer after hysterectomy and oophorectomy: a nationwide cohort study. Eur J Endocrinol. 2021; 184(1): 143–151, doi: 10.1530/EJE-20-0686, indexed in Pubmed: 33112277.
37. Guenego A, Mesrine S, Dartois L, et al. Relation between hysterectomy, oophorectomy and the risk of incident differentiated thyroid cancer: The E3N cohort. Clin Endocrinol (Oxf). 2019; 90(2): 360–368, doi: 10.1111/cen.13899, indexed in Pubmed: 30390407.
38. Falconer H, Yin Li, Bellocco R, et al. Thyroid cancer after hysterectomy on benign indications: Findings from an observational cohort study in Sweden. Int J Cancer. 2017; 140(8): 1796–1801, doi: 10.1002/ijc.30606, indexed in Pubmed: 28103650.
39. Altman D, Yin Li, Falconer H. Long-term cancer risk after hysterectomy on benign indications: population-based cohort study. Int J Cancer. 2016; 138(11): 2631–2638, doi: 10.1002/ijc.30011, indexed in Pubmed: 26800386.
40. Kabat GC, Kim MY, Wactawski-Wende J, et al. Menstrual and reproductive factors, exogenous hormone use, and risk of thyroid carcinoma in postmenopausal women. Cancer Causes Control. 2012; 23(12): 2031––2040, doi: 10.1007/s10552-012-0084-x, indexed in Pubmed: 23090034.
41. Braganza MZ, Berrington de González A, Schonfeld SJ, et al. Benign breast and gynecologic conditions, reproductive and hormonal factors, and risk of thyroid cancer. Cancer Prev Res (Phila). 2014; 7(4): 418–425, doi: 10.1158/1940-6207.CAPR-13-0367, indexed in Pubmed: 24449056.
42. Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D. Cancer: epidemiology and prevention. Oxford University Press, Oxford 2018.
43. Lewy-Trenda I. Estrogen and progesterone receptors in neoplastic and non-neoplastic thyroid lesions. Pol J Pathol. 2002; 53(2): 67–72, indexed in Pubmed: 12140869.
44. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. Hum Reprod Update. 2005; 11(4): 411–423, doi: 10.1093/humupd/dmi008, indexed in Pubmed: 15817524.
45. Kim JJ, Kurita T, Bulun SE. Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer. Endocr Rev. 2013; 34(1): 130–162, doi: 10.1210/er.2012-1043, indexed in Pubmed: 23303565.
46. Luoto R, Auvinen A, Pukkala E, et al. Hysterectomy and subsequent risk of cancer. Int J Epidemiol. 1997; 26(3): 476–483, doi: 10.1093/ije/26.3.476, indexed in Pubmed: 9222770.
47. Luoto R, Grenman S, Salonen S, et al. Increased risk of thyroid cancer among women with hysterectomies. Am J Obstet Gynecol. 2003; 188(1): 45–48, doi: 10.1067/mob.2003.121, indexed in Pubmed: 12548194.
48. Rossing MA, Voigt LF, Wicklund KG, et al. Reproductive factors and risk of papillary thyroid cancer in women. Am J Epidemiol. 2000; 151(8): 765–772, doi: 10.1093/oxfordjournals.aje.a010276, indexed in Pubmed: 10965973.
49. Wong EY, Ray R, Gao DL, et al. Reproductive history, occupational exposures, and thyroid cancer risk among women textile workers in Shanghai, China. Int Arch Occup Environ Health. 2006; 79(3): 251–258, doi: 10.1007/s00420-005-0036-9, indexed in Pubmed: 16220287.
50. Truong T, Orsi L, Dubourdieu D, et al. Role of goiter and of menstrual and reproductive factors in thyroid cancer: a population-based case-control study in New Caledonia (South Pacific), a very high incidence area. Am J Epidemiol. 2005; 161(11): 1056–1065, doi: 10.1093/aje/kwi136, indexed in Pubmed: 15901626.
51. Lundholm C, Forsgren C, Johansson ALV, et al. Hysterectomy on benign indications in Sweden 1987-2003: a nationwide trend analysis. Acta Obstet Gynecol Scand. 2009; 88(1): 52–58, doi: 10.1080/00016340802596017, indexed in Pubmed: 19140043.
52. Bíró J, Eneroth P, Ritzén EM. Effects of hysterectomy and in-vivo treatment with uterine extracts on plasma concentrations of growth hormone, thyrotrophin and thyroid hormones in rats: a kinetic study. J Endocrinol. 1984; 101(3): 243–248, doi: 10.1677/joe.0.1010243, indexed in Pubmed: 6726104.
53. Patak E, Pinto FM, Story ME, et al. Functional and molecular characterization of tachykinins and tachykinin receptors in the mouse uterus. Biol Reprod. 2005; 72(5): 1125–1133, doi: 10.1095/biolreprod.104.036814, indexed in Pubmed: 15647454.
54. Kim MH, Park YeR, Lim DJ, et al. The relationship between thyroid nodules and uterine fibroids. Endocr J. 2010; 57(7): 615–621, doi: 10.1507/endocrj.k10e-024, indexed in Pubmed: 20467159.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2024, vol. 95, no. 6, 443–450

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/gpl.95610

Neonatal outcomes for women diagnosed with cancer during pregnancy — single-center study

Beata Pawlus[1, 2], Jerzy Zwolinski[1, 2], Urszula Koneczna[1, 2], Grzegorz Pawlus[3], Agnieszka Kordek[4]

[1]Faculty of Medicine, Lazarski University, Warsaw, Poland
[2]Specialist Hospital of Holy Family, Warsaw, Poland
[3]Department of Physical Education, Academy of Physical Education and Sport, Gdansk, Poland
[4]Department of Neonatology and Neonatal Intensive Care Pomeranian Medical University in Szczecin, Poland

ABSTRACT

Objectives: Pregnancy complicated by cancer is one of the most serious challenges of modern perinatology. The increasing number of cancers diagnosed and treated during pregnancy requires a multidisciplinary approach to optimize the treatment of the person who is pregnant and deliver a healthy child. The aim of the study is to analyze the course of the neonatal period in children of mothers suffering from cancer during pregnancy, treated in a specialist hospital for women and children for ten years.

Material and methods: Retrospective observational study. Being diagnosed with cancer during pregnancy significantly increases the risk of premature delivery, prematurity and intrauterine growth restriction.

Results: Our own observations show no significant differences in the course of the neonatal period in children of mothers suffering from a malignant tumor during pregnancy compared to children of healthy mothers. This applies to both full-term and premature babies.

Conclusions: Modern treatment of malignant tumors during pregnancy seems to be safe for the fetus and newborn. It is optimal to conduct oncological, obstetric and neonatological treatment in one center. It seems advisable to conduct long-term follow-up observations in children of pregnant people with cancer. Since the described groups of patients and their newborns are small and heterogeneous, in order to develop appropriate standards, it is recommended to report these cases to central registers.

Keywords: newborn; pregnancy; cancer

Ginekologia Polska 2024; 95, 6: 443–450

INTRODUCTION

Pregnancy complicated by cancer is one of the most serious challenges for obstetricians and neonatologists. This leading to a difficult situation related to the care of the so-called "extended patient", *i.e.*, a newborn and the pregnant women.

"Pregnancy-related cancers" was defined as a diagnosis of malignancy from the time of pregnancy until 12 months after delivery. Most cases are diagnosed in the postpartum period, but the number of women diagnosed with cancer during pregnancy is steadily increasing. This is due to the increase in the incidence of malignant neoplasms in the entire population and the older age of pregnant women. Age is believed to be the main risk factor for developing cancer during pregnancy. The incidence of malignant neoplasms has increased in the female population over the last three decades by about 60%. It is estimated that cancer may occur in up to 1 in 1000 pregnant people worldwide [1].

A pregnant women diagnosed with a malignant tumor requires special multidisciplinary care (gynecologist–obstetrician, surgical oncologist, clinical oncologist/chemotherapist, psychologist, dietician, neonatologist, lactation

Corresponding author:
Agnieszka Kordek
Department of Neonatology and Neonatal Intensive Care Pomeranian Medical University in Szczecin, 2 Siedlecka St., 72-010 Police, Poland; phone: 501 197 941
e-mail: agnieszka.kordek@pum.edu.pl

Received: 17.05.2023 Accepted: 30.07.2023 Early publication date: 6.10.2023

consultant, physiotherapist) and a clear plan of therapeutic management with a presentation of risks and threats. For most patients, the main worry is fear for their own life and health, as well as the prognosis for the health and development of their child. The optimal solution is the possibility of treating the patient in one center, where complicated pregnancy can be managed, the patient can be operated on and treated with chemotherapy, the newborn can receive help adequate to the stage of pregnancy, and the women can receive lactation and psychological care. If it is necessary to terminate the pregnancy prematurely (usually due to the condition of the patient and continuation of their treatment, the newborn and mother can be treated in one center, which allows for at least limited but possible contact between parent and child. The newborn may, in addition to highly specialized neonatological treatment, receive modern nutritional treatment in the form of breast milk from a milk bank for the period of stabilization of the general condition and/or the mother's possible return to breastfeeding [2]. Such an interdisciplinary approach reduces the level of anxiety in the patient, increases the level of safety and, above all, positively affects the long-term effects of treatment for both the pregnant women and the child in this clinically and psychologically difficult situation [3, 4].

It should be remembered that therapeutic management in pregnancy complicated by malignancy should consider not only medical indications, but also the patient's preferences and important ethical and religious aspects, including decisions to continue the pregnancy in the context of a threat to health and life. Studies show that termination of pregnancy does not improve prognosis in patients diagnosed with malignancy during pregnancy. The International Network on Cancer, Infertility and Pregnancy (INCIP) recommends oncological treatment while maintaining pregnancy [5, 6], although we find retrospective cohort studies showing that, in the group of women diagnosed with cancer, decisions about abortion/induced miscarriage were more frequent than in the control group [7]. The prognosis for patients diagnosed with cancer during pregnancy is similar to that for non-pregnant women at the same stage of cancer. Appropriately selected therapy does not pose a risk to the fetus and further development of the child, nor does it diminish its effectiveness [5, 8].

Pregnancy is not a contraindication to anticancer surgical treatment [8]. Most malignant solid tumors require surgical treatment. Both the procedure and the anesthesia may have adverse effects on the fetus. Anesthetics do not increase the risk of congenital defects, but their use in the first trimester of pregnancy carries the risk of miscarriage. It is recommended to perform operations in the II and III trimesters of pregnancy. After the 24th week of pregnancy, the well-being of the fetus should be monitored during the procedure, and the patient should be warned about the possibility of performing a cesarean section in the event of a threat to the life of the child [3, 4, 6].

The use of cytostatic drugs during the first trimester of pregnancy is associated with a high risk of fetal damage, but most cytotoxic drugs can be safely used in the second and third trimester of pregnancy, considering the specificity of the pregnancy period (larger plasma volume, lower albumin concentration, altered renal and hepatic function). Therefore, chemotherapy can be used in the second and third trimesters of pregnancy, but usually not longer than 34–35 weeks of pregnancy, with a 3-week break in therapy before the planned termination of pregnancy (if there is no need for early termination of pregnancy due to maternal indications). This is dictated by the limitation of the effect of drugs on the condition of the newborn, because almost all cytostatic drugs cross the placental barrier. The decision to start radiotherapy in pregnant women should be made only in special cases, as in principle it is not used in the treatment of pregnancy-related cancers [5, 6, 9].

Childbirth in a pregnancy complicated by malignant tumor should, if possible, take place as in healthy individuals, by natural means. After a natural birth, oncological treatment can be started faster — chemotherapy after a natural delivery is possible almost immediately, and after an uncomplicated caesarean section, after about a week. The decision to perform caesarean section may be made based on obstetric or oncological indications [6, 10–12]. Breastfeeding of a newborn by a pregnant woman suffering from a malignant tumor during pregnancy is possible. The decision not to start or stop breastfeeding is always up to the patient. However, it should be remembered that breastfeeding is contraindicated during radiotherapy and chemotherapy, which is possible after birth. Cytostatics pass into breast milk, causing leukopenia. Breastfeeding can be started two weeks after the end of chemotherapy [5, 13].

Cancer epidemiology in pregnancy varies slightly from region to region. The reports mention various cancers diagnosed in pregnant women: breast, cervical and ovarian, thyroid, colorectal, hematopoietic system, Hodgkin's lymphoma, melanoma, and brain tumors. Breast cancer is the most common malignancy diagnosed in pregnancy worldwide. Around 10,000 people worldwide suffer from breast cancer during pregnancy every year [1, 5, 13, 14]. Breast cancer in pregnant women is usually diagnosed at a more advanced stage than in the non-pregnant population. The growing lump in the breast is treated as a physiological response of the glandular tissue to hormonal changes associated with pregnancy. Women in general, but also doctors, do not realize that breast cancer can occur in a young pregnant woman. Diagnosis in pregnant women is delayed by 2–7 months from the moment the first symptoms appear. Delay-

ing the diagnosis by six months results in an increase in the number of patients with regional lymph node metastases by over 5% [5, 13, 14]. Breastfeeding is possible and safe after the diagnosis and treatment of breast cancer, although the literature in this area is scarce and is based on only a few groups of patients. Breastfeeding counseling and planning are key factors in maintaining and prolonging lactation in women with breast cancer. However, despite this, about half of breast cancer patients choose not to breastfeed or express their own milk. Breastfeeding usually involves a healthy breast. The reasons for not trying to feed from an affected breast are usually difficulty in suckling, reduced milk production and breast pain. There are no differences in the frequency of recurrence of the disease in the group of women who are breastfeeding and those who give up breastfeeding [5, 13].

The aim of the study was to summarize the ten-year own observations of neonatal outcomes for women diagnosed with cancer during pregnancy.

MATERIAL AND METHODS

A retrospective analysis covered the course of the neonatal period of children born to pregnant women suffering from malignant tumors over 10 years (2012–2021) in a multispecialty reference center (Specialistic Hospital of the Holy Family, Warsaw, Poland). During this period, 52.088 deliveries took place in the hospital. A total of 399 cases of tumors during pregnancy were diagnosed, including 379 benign tumors and 20 cases of cancers. Pregnant women suffering from malignant cancer, who were treated oncologically during pregnancy and gave birth to newborns accounted for 0.04% of all patients giving birth in the hospital in this period. It is adequate in relation to the data from the literature, *i.e.*, 0.02–0.1% of all pregnancies [1]. The Specialist Hospital Holy Family in Warsaw is a reference center for the region, focused on comprehensive diagnostics and the treatment of women and their children. It has modern departments in its structure, including obstetrics, neonatology, pediatrics, oncological gynecology, oncological surgery, clinical oncology and a regional breast milk bank. In addition to specialist neonatal care with the possibility of intensive care and treatment at the neonatal pathology ward, further care and follow-up at the pediatric ward is possible.

The source of information was medical records. Each case of cancer diagnosed during pregnancy was analyzed. The small size of the group and its heterogeneity limited the possibility of statistical analysis.

RESULTS

Among the twenty analyzed cases, seven cases of breast cancer, five cases of thyroid cancer and a single case of cervical cancer, ovarian cancer, Hodgkin's lymphoma, lymphoblastic leukemia, colorectal cancer, anal cancer, sarcoma and fibromatosisdesmoid were diagnosed and treated. The patients' age, oncological diagnosis, course of pregnancy, method of delivery, fetal age, birth weight of newborns, and course of the neonatal period are shown in Table 1. The age of the patients ranged from 19 to 36 years (mean 30.5 years). In our study group, 12 newborns (60%) were born by caesarean section. In this hospital, the caesarean section rate in the entire patient population is quite high at 50%. Oncological indications for the caesarean section were observed in the following five cases: cervical cancer and advanced neoplastic processes in patients with ovarian, rectal, sigmoid, and Hodgkin's lymphoma.

Although, cervical cancer is one of the most common in women of reproductive age, only one of the women in our study had stage IIA1 cervical cancer. Due to the previous caesarean section and the oncological condition, the pregnancy was terminated by caesarean section at the time of delivery (41 weeks of gestation). Radical surgical treatment was performed after the birth of the child [14].

Additionally, one case of ovarian cancer occurred among our patients. The pregnancy was terminated prematurely by caesarean section due to oncological indications. Radical surgical treatment was performed after the child was extracted [15].

Newborns of mothers with pregnancy-related cancer were born at a gestational age of 24 to 41 weeks, the mean 36.1. In total, 7/20 newborns were born prematurely — 35% (Tab. 1). In the Polish population, the percentage of prematurity in those years was between 6-7%. Late premature babies — 5/7, 2 were born below 32 weeks gestation (29 and 24). Both mothers of the most immature children died in the first year after delivery — they presented the most advanced cancer process, and the decision to end pregnancy prematurely was dictated by the mothers' health condition. A significantly increased percentage of prematurity in the group of newborns born to mothers with cancer during pregnancy, consistent with the reports of other authors, is iatrogenic. The decision to terminate pregnancy prematurely is dictated by oncological indications and the need to treat the mother [1, 16–19]. In the study "Pregnancy and Cancer: the INCIP Project" published in 2020, based on the data register from the International Network on Cancer, Infertility and Pregnancy (INCIP) database, the authors report up to 47% prematurity in the group of newborns born to mothers with malignant tumors during pregnancy, of which one third are newborns born before 34 weeks of gestation [6] (Tab. 1).

DISCUSSION

Among the analyzed newborns, 5/20 were born with a low birth weight (LBW) below 2500 g, including one newborn with a very low birth weight (VLBW) and one with an

Table 1. The course of pregnancy and the neonatal period

Mother's age [years]		Parity G/P	Diagnosis	Week of gestation	The course of pregnancy	Mode of delivery	Birth weigh [g]	APGAR 1′/5′/10′	The course of the neonatal period, hospital stay
NS	26	I/I	Breast cancer	37	After mastectomy at 25 weeks of gestation, during chemotherapy, failed induction of labor	Cesarean	3757	10/10/10	Healthy newborn Cavernous hemangioma No complications 4 days
IO	34	I/I	Breast cancer	39	After mastectomy, during chemotherapy, state after CS	Vaginal	3185	10/10/10	Healthy newborn No complications 3 days
MR	36	II/II	Breast cancer	40	Invasive cancer, diagnosis in the first trimester, no consent to treatment, thrombocytopenia	Vaginal	2860	10/10/10	Healthy newborn No complications 3 days
EW	32	III/II	Breast cancer	37	After mastectomy at 24 weeks of gestation, during chemotherapy	Vaginal	3350	10/10/10	Healthy newborn Hyperbilirubinemia phototherapy typical course 6 days
HK	36	II/II	Breast cancer	37	After mastectomy in the first trimester, GDMG1, IUGR, placental failure, feto-maternal shunt, depression; no consent to treatment chemotherapy,	Cesarean	2430	3/2/2	Perinatal asphyxia, baby-maternal transfusion syndrome, congenital anemia, hepatosplenomegaly, thrombocytopenia, neutropenia, cholestasis NICU 19 days
MK	35	IV/III	Breast cancer	36	After a mastectomy in the first trimester, no consent to treatment chemotherapy, state after CS	Cesarean	2840	10/10/10	Prematurity, adaptive breathing disorders, HFNC 1 day typical course 5 days
PW	31	I/I	Breast cancer	40	Before oncological treatment	Vaginal	3625	10/10/10	Healthy newborn No complications 3 days
ML	25	II/I	Thyroid cancer	39	Condition after strumectomy, oligohydramnios	Vaginal	2675	10/10/10	VSD, hypotrophy, hyperbilirubinemia-phototherapy typical course 5 days
PB	35	III/II	Thyroid cancer	38	Condition after strumectomy	Vaginal	4036	10/10/10	Healthy newborn No complications 3 days
KD	29	III/I	Thyroid cancer	38	Condition after strumectomy, Pelvic position of the fetus; GDMG2, PROM	Cesarean	3355	10/10/10	Healthy newborn No complications 3 days
MS	30	II/I	Thyroid cancer	39	Condition after strumectomy,	Vaginal	3580	10/10/10	Healthy newborn No complications 3 days
MP	34	I/I	Thyroid cancer	37	Condition after strumectomy, deep vein thrombosis, polyhydramnios	Cesarean	3325	8/10/10	Pneumonia, respiratory failure, pneumothorax, Mechanical ventilation, cardiac arrhythmias NICU 10 days

→

Table 1. cont. The course of pregnancy and the neonatal period

Mother's age [years]		Parity G/P	Diagnosis	Week of gestation	The course of pregnancy	Mode of delivery	Birth weigh [g]	APGAR 1′/5′/10′	The course of the neonatal period, hospital stay
IK	28	III/II	Cervical cancer	41	Diagnosis II trimester, anemia; surgical treatment after childbirth; State after CS Oncological indications for CS	Cesarean	3024	10/10/10	Skull bone defect, neonatal period without complications 5 days
MB	23	I/I	Ovarian cancer	34	CS with removal of the appendages and greater omentum, the need for treatment Oncological indications for CS	Cesarean	2290	8/8/8	Healthy newborn Hyperbilirubinemia-phototherapy, typical course 10 days
BD	29	II/I	Hodgkin lymphoma	34	During chemotherapy, the need for further treatment Oncological indications for CS	Cesarean	2736	10/10/10	Prematurity, respiratory failure, RDS II, NICU 5 days
SD	19	I/I	Lymphoblastic leukemia, bilateral breast and ovarian tumors, mediastinal changes	24	Disseminated neoplastic process, diagnosis in the second trimester, postpartum chemotherapy, death in the first year	Vaginal	500	2/2/4	Extreme prematurity, respiratory failure, circulatory failure, PDA, IVH II, convulsions, late onset sepsis, BPD, ROP II, right ovarian cyst NICU 141 days
KM	28	II/II	Colorectal (sigmoid) cancer, metastases to the ovaries and liver, infiltration of the cervix, right parametrium and paravagina	29	Disseminated neoplastic process, palliative chemotherapy, low gastro-intestinal obstruction at 29 weeks gestation, single-barrel end stoma during CS, death in the first year Oncological indications for CS	Cesarean	1490	9/10/9	Prematurity, respiratory failure, hyperbilirubinemia-phototherapy NICU 44 days
JZ	34	II/II	Anal cancer	35	Operation in the 17th week; depression, the need for further treatment Oncological indications for CS	Cesarean	2540	10/10/10	Prematurity, VSD, perinatal adaptation disorders, nCPAP 5 days
KK	32	III/II	Sarcoma	37	Condition after chest reconstruction, GDMG2, PROM	Cesarean	3165	10/10/10	Healthy newborn No complications 3 days
PS	34	III/III	Recurrent desmoid tumors	36	Relapse in pregnancy; removal of the tumor of the 7th rib and the latissimus dorsi muscle in the 2nd trimester — (fibromatosisdesmoid-type), state after CS, FGR I$_{st}$	Cesarean	2025	10/10/10	Prematurity, hypotrophy, mild opioid withdrawal syndrome 11 days

G/P — gestation/parturition; GDMG — gestational diabetes mellitus; IUGR — Intrauterine growth restriction; FGR — fetal growth restriction; PROM — premature rupture of membranes; CS — cesarean section; VSD — ventricular septal defect; RDS — respiratory distress syndrome; PDA — patent ductus arteriosus; IVH — intraventricular hemorrhage; ROP — retinopathy of prematurity; BPD — bronchopulmonary dysplasia; NICU — Neonatal Intensive Care Unit; HFNC — high flow nasal cannula; nCPAP — nasal continuous positive airway pressure

extremely low birth weight extremely low birth weight (ELBW). The authors point out the risk of fetal growth retardation intrauterine growth retardation (IUGR) and fetal hypotrophy (SGA-small for gestational age) in the group of newborns of mothers with cancer during pregnancy, especially when the pregnant woman is treated with chemotherapy [6, 20, 21]. We suggest ensuring the careful monitoring of the well-being of the fetus and the decision to complete the pregnancy at 35–36 weeks gestation as the safest for a newborn at risk of IUGR [22, 23].

Only two newborns in our group could be included in the SGA group. One of them was diagnosed with a congenital heart defect — ventricular septal defect (VSD), which means that the cause of hypotrophy was not fully attributed to the mother's cancer. The second case is a premature baby, 36 weeks gestation, mother with recurrent desmoid disease, recurrence of the disease during pregnancy, removal of a tumor of the left seventh rib and the latissimus dorsi muscle in the second trimester of pregnancy, maternal hypertension and chronic use of opioids for analgesic treatment. The causes of hypotrophy seem to be complex in this clinical situation. However, the register data of the International Network on Cancer, Infertility and Pregnancy (INCIP) show that up to 21% of newborns born to mothers with cancer during pregnancy may be born too small for their gestational age (SGA) [6].

Two newborns in the analyzed group were diagnosed with a heart defect. In both cases, heart defects were detected in the form of a defect in the interventricular septum, without significant hemodynamic disturbances and the need for intervention. Few authors have tried to search for a relationship between oncological treatment during pregnancy and heart defects in the fetus and newborn. Most pregnant cancer patients undergo chemotherapy treatment in the second or third trimester of pregnancy, after the period of organogenesis, and such a relationship has not been proven [23]. However, there are still numerous studies evaluating the impact of chemotherapy and/or growth factor support during pregnancy on fetal development, in a broader sense than just the risk of development defects. Although the results are reassuring, the number of cases remains understandably limited, and continuous surveillance of patients and their newborns is warranted [24, 25]. One of the newborns was diagnosed with a skull bone defect and one with a cavernous hemangioma. A review of the literature does not indicate such cases; therefore, these diagnoses seem to be unrelated to maternal cancer.

The length of neonatal hospitalization depended on their maturity and the resulting problems of prematurity. Full-term infants (n = 13) were usually discharged between the third and fifth day of life (n = 11), which is the standard adopted in our hospital. One neonate born by caesarean section for obstetric reasons after the end of the 37th week of pregnancy was discharged after 19 days for reasons unrelated to maternal breast cancer treated surgically in the first trimester of pregnancy. Due to perinatal complications (baby–maternal transfusion syndrome, severe anemia, perinatal asphyxia, IUGR), the child required treatment at the Neonatal Intensive Care Unit (NICU) for several days. Another newborn born by caesarean section due to deep vein thrombosis in the mother after the end of the 37th week of pregnancy was discharged after 10 days due to neonatal complications (pneumonia, pneumothorax, arrhythmia). The child required treatment with mechanical ventilation for five days in the NICU.

Three more newborns required treatment in the NICU: a newborn with ELBW (500 g) born at 24 weeks of gestation and a newborn born at 29 weeks of gestation, as well as a newborn born at 34 weeks of gestation who developed respiratory distress syndrome (RDS) II degree. These five children required respiratory support. No newborns died.

The course of the neonatal period of children of mothers suffering from malignant neoplasm during pregnancy, was completely uncomplicated in most children. Out of the thirteen full-term newborns, one was diagnosed and treated with congenital pneumothorax, and one was treated with severe congenital anemia during the mother–child transfusion syndrome. There was no association with maternal cancer. The remaining full-term newborns did not present any disturbances in the neonatal period. In all prematurely born newborns, typical and appropriate disorders were observed, ranging from mild adaptation disorders in the so-called late premature infants to serious diseases associated with extreme prematurity (details in Tab. 1) — as in newborns of mothers not suffering from cancer during pregnancy. In the few available studies analyzing the course of the neonatal period and infancy, the authors indicate no differences during the neonatal period of children of pregnant mothers with cancer compared to children of healthy mothers [11]. The most common complication in the perinatal period associated with the use of chemotherapy in the patient is myelosuppression of various degrees, which in most cases is transient [23]. Follow-up of children of mothers suffering from cancer during pregnancy in terms of cognitive disorders shows that the disorders result only from prematurity, and they are comparable to children born in the same period of pregnancy without chemotherapeutic treatment — no differences between the groups were found. The cognitive development of children of mothers with cancer should be considered undisturbed [23, 26]. This is confirmed by our own observations during routine examinations in the outpatient clinic.

CONCLUSIONS

Being diagnosed with cancer during pregnancy significantly increases the risk of premature delivery, prematurity and intrauterine growth restriction (IUGR). However, our own observations show no significant differences during the neonatal period in children of pregnant mothers with malignant tumors compared to children of healthy mothers. This applies to both full-term and premature babies. The treatment of malignant tumors during pregnancy seems to be safe for the fetus and newborn. It is optimal to conduct oncological, obstetric and neonatological treatment in one center. It seems advisable to conduct at least several years of follow-up in children of pregnant mothers with cancer. Since the described groups of patients and their newborns are small and heterogeneous, in order to develop appropriate standards, it is recommended to report these cases to the INCIP registry.

Article information and declarations

Data availability statement

All data available from the authors.

Ethics statement

Retrospective research on material based on established and recognized routine methods of treatment does not bear the hallmarks of a medical experiment and does not require the consent of the bioethics committee, which results from the Act on the professions of doctor and dentist (according to the opinion of the University of Gdansk of Physical Education and Sport' Bioethics Committee).

Author contributions

Beata Pawlus: conception, assumption article, draft revision; Jerzy Zwolinski: aquisition of data, assumption; Urszula Koneczna: aquisition of data; Grzegorz Pawlus: analysis and interpretation of data, article draft; Agnieszka Kordek: draft revision, corresponding author.

Funding

Without external financing, statutory activities of the university (Pomeranian Medical University in Szczecin).

Acknowledgments

None.

Conflict of interest

None.

Supplementary material

None.

REFERENCES

1. Dalmartello M, Negri E, La Vecchia C, et al. Frequency of Pregnancy-Associated Cancer: A Systematic Review of Population-Based Studies. Cancers (Basel). 2020; 12(6), doi: 10.3390/cancers12061356, indexed in Pubmed: 32466494.
2. Kontopodi E, Arslanoglu S, Bernatowicz-Lojko U, et al.„Donor milk banking: Improving the future". A survey on the operation of the European donor human milk banks. PLoS One. 2021; 16(8): e0256435, doi: 10.1371/journal.pone.0256435, indexed in Pubmed: 34411191.
3. Silverstein J, Post AL, Chien AJo, et al. Multidisciplinary Management of Cancer During Pregnancy. JCO Oncol Pract. 2020; 16(9): 545–557, doi: 10.1200/OP.20.00077, indexed in Pubmed: 32910882.
4. Cubillo A, Morales S, Goñi E, et al. Multidisciplinary consensus on cancer management during pregnancy. Clin Transl Oncol. 2021; 23(6): 1054––1066, doi: 10.1007/s12094-020-02491-8, indexed in Pubmed: 33191439.
5. Boere I, Lok C, Poortmans P, et al. Breast cancer during pregnancy: epidemiology, phenotypes, presentation during pregnancy and therapeutic modalities. Best Pract Res Clin Obstet Gynaecol. 2022; 82: 46–59, doi: 10.1016/j.bpobgyn.2022.05.001, indexed in Pubmed: 35644793.
6. Maggen C, Wolters VE, Cardonick E, et al. International Network on Cancer, Infertility and Pregnancy (INCIP). Pregnancy and Cancer: the INCIP Project. Curr Oncol Rep. 2020; 22(2): 17, doi: 10.1007/s11912-020-0862-7, indexed in Pubmed: 32025953.
7. Greiber IK, Viuff JH, Mellemkjaer L, et al. Cancer in pregnancy and the risk of adverse pregnancy and neonatal outcomes: A nationwide cohort study. BJOG. 2022; 129(9): 1492–1502, doi: 10.1111/1471-0528.17074, indexed in Pubmed: 34954890.
8. Hepner A, Negrini D, Hase EA, et al. Cancer During Pregnancy: The Oncologist Overview. World J Oncol. 2019; 10(1): 28–34, doi: 10.14740/wjon1177, indexed in Pubmed: 30834049.
9. Korenaga TRK, Tewari KS. Gynecologic cancer in pregnancy. Gynecol Oncol. 2020; 157(3): 799–809, doi: 10.1016/j.ygyno.2020.03.015, indexed in Pubmed: 32268951.
10. Puzzi-Fernandes C, Surita FG, Schettini CS, et al. Awareness towards an increasing concern during pregnancy: maternal and perinatal outcomes of women with cancer. Am J Obstet Gynecol MFM. 2020; 2(3): 100168, doi: 10.1016/j.ajogmf.2020.100168, indexed in Pubmed: 33345887.
11. Yp Z, J D, Xw Z, et al. Maternal and neonatal outcomes of cancer during pregnancy: a multi-center observational study. J Cancer. 2019; 10(23): 5727–5734, doi: 10.7150/jca.33746, indexed in Pubmed: 31737109.
12. Folsom SM, Woodruff TK. Good news on the active management of pregnant cancer patients. F1000Res. 2020; 9, doi: 10.12688/f1000research.22472.1, indexed in Pubmed: 32528657.
13. Peccatori FA, Migliavacca Zucchetti B, Buonomo B, et al. Lactation during and after Breast Cancer. Adv Exp Med Biol. 2020; 1252: 159–163, doi: 10.1007/978-3-030-41596-9_22, indexed in Pubmed: 32816277.
14. Monti M, D'Aniello D, Scopelliti A, et al. Relationship between cervical excisional treatment for cervical intraepithelial neoplasia and obstetrical outcome. Minerva Obstet Gynecol. 2021; 73(2): 233–246, doi: 10.23736/S2724-606X.20.04678-X, indexed in Pubmed: 33140628.
15. Bogani G, Ditto A, Pinelli C, et al. Ten-year follow-up study of long-term outcomes after conservative surgery for early-stage ovarian cancer. Int J Gynaecol Obstet. 2020; 150(2): 169–176, doi: 10.1002/ijgo.13199, indexed in Pubmed: 32415982.
16. Kalampokas E, Vlahos N, Kalampokas T, et al. Common Malignancies During Pregnancy: A Comprehensive Review. Cancer Diagn Progn. 2021; 1(3): 103–109, doi: 10.21873/cdp.10015, indexed in Pubmed: 35399318.
17. Ray JG, Vermeulen MJ, Bharatha A, et al. Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes. JAMA. 2016; 316(9): 952–961, doi: 10.1001/jama.2016.12126, indexed in Pubmed: 27599330.
18. Bhurosy T, Niu Z, Heckman CJ. Breastfeeding is Possible: A Systematic Review on the Feasibility and Challenges of Breastfeeding Among Breast Cancer Survivors of Reproductive Age. Ann Surg Oncol. 2021; 28(7): 3723–3735, doi: 10.1245/s10434-020-09094-1, indexed in Pubmed: 32915334.
19. Maggen C, Dierickx D, Cardonick E, et al. International Network on Cancer Infertility Pregnancy (INCIP). Maternal and neonatal outcomes in 80 patients diagnosed with non-Hodgkin lymphoma during pregnancy: results from the International Network of Cancer, Infertility and Pregnancy. Br J Haematol. 2021; 193(1): 52–62, doi: 10.1111/bjh.17103, indexed in Pubmed: 32945547.

20. Esposito G, Franchi M, Dalmartello M, et al. Obstetric and neonatal outcomes in women with pregnancy associated cancer: a population-based study in Lombardy, Northern Italy. BMC Pregnancy Childbirth. 2021; 21(1): 31, doi: 10.1186/s12884-020-03508-4, indexed in Pubmed: 33413225.
21. Maxwell CV, Al-Sehli H, Parrish J, et al. Breast Cancer in Pregnancy: A Retrospective Cohort Study. Gynecol Obstet Invest. 2019; 84(1): 79–85, doi: 10.1159/000493128, indexed in Pubmed: 30219806.
22. Lu D, Ludvigsson JF, Smedby KE, et al. Maternal Cancer During Pregnancy and Risks of Stillbirth and Infant Mortality. J Clin Oncol. 2017; 35(14): 1522––1529, doi: 10.1200/JCO.2016.69.9439, indexed in Pubmed: 28384079.
23. Maggen C, Wolters VE, Van Calsteren K, et al. International Network on Cancer, Infertility and Pregnancy (INCIP). Impact of chemotherapy during pregnancy on fetal growth. J Matern Fetal Neonatal Med. 2022; 35(26): 10314–10323, doi: 10.1080/14767058.2022.2128645, indexed in Pubmed: 36202393.
24. Sorokine A, Czuzoj-Shulman N, Abenhaim HA. Maternal and neonatal outcomes in women with a history of chemotherapy exposure: a population-based study of 8 million obstetric admissions. Arch Gynecol Obstet. 2023; 307(3): 747–753, doi: 10.1007/s00404-022-06566-5, indexed in Pubmed: 35523971.
25. Sella T, Exman P, Ren S, et al. Outcomes after treatment of breast cancer during pregnancy including taxanes and/or granulocyte colony-stimulating factor use: findings from a multi-institutional retrospective analysis. Breast Cancer Res Treat. 2022; 194(3): 597–606, doi: 10.1007/s10549-022-06621-4, indexed in Pubmed: 35715538.
26. de Haan J, Verheecke M, Van Calsteren K, et al. International Network on Cancer and Infertility Pregnancy (INCIP). Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol. 2018; 19(3): 337–346, doi: 10.1016/S1470-2045(18)30059-7, indexed in Pubmed: 29395867.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2024, vol. 95, no. 6, 451–459

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/gpl.96919

Clinicopathologic characteristics, treatment, prognosis and pregnancy outcomes in rhabdomyosarcoma of the uterine cervix: a case series

Xiuzhang Yu[1, 2], Mingrong Qie[1, 2], Liyan Huang[3], Minmin Hou[1, 2]

[1]Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, China
[2]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, China
[3]Department of Pathology, West China Second University Hospital, Sichuan University, Chengdu, China

ABSTRACT

Objectives: In this retrospective observational study, cases from our institution were included and the published literature reviewed to investigate the diagnosis and prognosis of cervical rhabdomyosarcoma, a rare group of tumours.

Material and methods: The clinicopathological data of 12 patients with cervical rhabdomyosarcoma (RMS) treated at the West China Second University Hospital of Sichuan University from January 2006 to May 2023 were collected, and their clinicopathological characteristics, diagnoses, treatments, prognoses and pregnancy outcomes were retrospectively analysed.

Results: (1) Clinical characteristics: The ages of the 12 RMS patients ranged from 15 to 50 years, with a median age of 17 years. Five of the patients were adults, and seven were adolescents. The initial symptoms were vaginal bleeding in 5 patients, vaginal tissue prolapse in 6 patients, and abdominal pain and urinary frequency in 1 patient. Two patients were considered to have "cervical polyps" and underwent polypectomy at the other hospitals, but the cervical mass recurred soon thereafter. (2) Pathological features: The maximum tumour diameter ranged from 3 to 25 cm. The twelve cases of cervical RMS consisted of embryonal rhabdomyosarcoma (ERMS) in 7 adolescents, ERMS in 3 adults, and pleomorphic rhabdomyosarcoma (PRMS) in 2 adults. Immunohistochemical results showed the expression of one or more characteristic markers of RMS. We reclassified tumour stage according to the Intergroup Rhabdomyosarcoma Study (IRS) clinical group and tumour node metastasis (TNM) classification. (3) Treatment: Eight patients underwent radical surgery (66.7%, 8/12), including all 5 of the included adults and 3 of the adolescents, 2 of whom were treated 10 years ago. Conservative surgical resection was performed on four patients (33.3%, 4/12), all of whom were adolescents. Postoperative chemotherapy was given to all patients except one, but one patient who underwent radical surgery discontinued chemotherapy on her own without receiving a full course. Two of the ERMS patients underwent preoperative chemotherapy, and the lesions were significantly reduced. (4) Prognosis: One of the 12 patients with cervical RMS was lost to follow-up. Of the remaining 11 patients, 10 (including seven adolescents and three adults) survived tumour free (90.9%, 10/11), and 1 adult patient with existing pulmonary multiple metastases (IRS stage IV, T2N0M1) at the initial diagnosis survived 9 months with progression-free disease (9.1%, 1/11). The median survival time was 91 months (5 to 213 months). Among 4 patients receiving fertility-sparing management, 1 conceived and delivered successfully (25%).

Conclusions: The treatment of cervical RMS must take the patient's age and reproductive intent into account. The overall prognosis for cervical RMS in children and adolescents is good, and conservative surgical resection combined with chemotherapy is recommended to preserve fertility. The pregnancy outcome is also worth anticipating. For patients who have completed childbirth, radical surgery is preferred. Approaches to accurately assessing the patient's condition, grasping the indications and scope of surgery, and developing chemoradiotherapy regimens deserve further exploration.

Keywords: cervical sarcoma; rhabdomyosarcoma; fertility preservation; chemotherapy; prognosis

Ginekologia Polska 2024; 95, 6: 451–459

Corresponding author:
Minmin Hou
Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Number 20, 3rd section, South Renmin Road, Chengdu, Sichuan 610041, China
e-mail: mminnh789@163.com

Received: 11.08.2023 Accepted: 23.11.2023 Early publication date: 20.12.2023

INTRODUCTION

Rhabdomyosarcoma (RMS) represents a rare group of tumours that are classified into four major subtypes according to the 2020 WHO Soft Tissue Tumour Classification: embryonal rhabdomyosarcoma (ERMS), alveolar rhabdomyosarcoma (ARMS), spindle cell/sclerosing rhabdomyosarcoma, and pleomorphic rhabdomyosarcoma (PRMS). Among these, ERMS is the most common type, usually occurring in the mucosa or near the mucosa of the head, orbit, or lower genitourinary tract. Only 0.5% of primary RMSs are located in the cervix, and they usually appear in the first two decades of life. Cervical RMS that appears in adults is even rarer [1]. Most of the current knowledge about RMS comes from case reports, clinical studies by the Intergroup Rhabdomyosarcoma Study Group (IRSG) and Children's Oncology Group (COG), and the consensus of the International Soft-Tissue Sarcoma Consortium (INSTRuCT) [2]. Clinical studies of female genital tract RMS are primarily in children; there is a lack of prospective studies of adult female genital tract RMS, and there are only a few reported cases of adult cervical RMS (fewer than 40 cases) [3]. The therapeutic regimen is based mainly on the experience of RMS at sites other than the cervix. Paediatric RMS appears to have a better prognosis than adult RMS [4]. We clinically analysed 12 patients with cervical RMS treated at the West China Second University Hospital of Sichuan University from January 2006 to May 2023, and we discuss the clinicopathologic features, treatments, prognoses and pregnancy outcomes of this disease in the context of the relevant literature, with the objective of improving the diagnosis and treatment experience of this disease.

MATERIAL AND METHODS

Patients with cervical RMS were treated at the West China Second University Hospital of Sichuan University from January 2006 to May 2023. The study was conducted following the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the West China Second University Hospital, and informed consent was obtained from all patients.

The inclusion criteria were as follows: 1) patients with a confirmed pathological diagnosis of cervical RMS; 2) patients with both pathological consultation records and clinical consultation records; and 3) patients diagnosed with cervical rhabdomyosarcoma that was not part of a biphasic tumour or germ cell tumour and with a pathology report confirming that the tumour did not originate elsewhere (*e.g.*, the uterus).

The general data, clinical manifestations, auxiliary examinations, pathological features, treatment modalities and prognoses of the patients were retrospectively analysed. Follow-up was also performed by telephone. The follow-up cut-off date was October 15, 2023. The follow-up period ranged from 5 to 213 months, with a median follow-up time of 91 months. One patient was lost to follow-up. The limitation and bias of this study is the small number of cases, but a large-scale study of this rare disease is not possible.

RESULTS

Clinical characteristics: The ages of the 12 patients with cervical RMS ranged from 15 to 50 years, with a median of 17 years (the youngest patient with female genital tract RMS at our hospital was two months old and was not included in this study because she did not receive clinical treatment). There were 7 adolescent patients and 5 adult patients. One patient had the "congenital pulmonary cyst", and two patients had the "thyroid cyst". Three patients had a family history of tumours. The initial symptoms were vaginal bleeding in 5 patients, vaginal tissue prolapse in 6 patients, and abdominal pain and urinary frequency in 1 patient. Two patients were considered to have "cervical polyps" and underwent polypectomy at other hospitals, but the cervical mass recurred soon thereafter (Tab. 1). Patients 4, 5, 6, and 7 underwent magnetic resonance imaging (MRI), and patients 2, 3, 8, 9, 10, 11, and 12 underwent computed tomography (CT). The results of the examinations were consistent with the B-ultrasonography findings, and there was no specificity. The lung CT of Patient 11 indicated multiple lung metastases.

Pathological characteristics: The lesions of the included patients were located at the cervix/cervical junction. The maximum tumour diameter ranged from 3 to 25 cm. We obtained the MR images of patient 6, as shown in Figure 1. The immunohistochemical findings revealed the expression of one or more characteristic markers of RMS, including vimentin (Vim), desmin, myoglobin (Mb), myogenin, and myogenic differentiation protein (MYOD), as shown in Table 2. Among the 12 patients with cervical RMS, all the adolescent patients had ERMS, one of whom had embryonal rhabdomyosarcoma (differentiated) with chondrogenesis and one of whom had ERMS with the focal area containing the adenoid rhabdomyosarcoma component. Three patients underwent genetic testing. The patient with ERMS combined with ARMS had no meaningful FOXO1 (FKHR) gene allele detected, and 2 patients with ERMS who underwent DICER1 genetic testing had a 50% mutation rate (1/2). The pathologic characteristics of patient 6, a 17-year-old patient with typical cervical ERMS, are shown in Figure 2. Three of the adult patients had ERMS, and two, aged 49 and 50 years, had PRMS. Details are shown in Table 2.

Treatment approaches: 1) of the 7 adolescent patients included in this study, 3 underwent radical surgery, two of whom were treated 10 years ago, and the other, whose

Table 1. Clinical features of 12 patients with cervical rhabdomyosarcoma (RMS)

No	Age [yr]	BMI [kg/m^2]	Parity (at first visit)	Age of menarche	History of surgery and previous illnesses	Family history of cancer	Initial symptom
1	17	Unknown	G0P0	13	None	None	Vaginal tissue prolapse
2	17	17.9	G0P0	13	Surgery for "pulmonary cyst"	None	Vaginal bleeding
3	17	21.9	G0P0	12	Excision of left ovarian cyst	None	Vaginal bleeding
4	17	20.5	G0P0	12	None	Head cancer (mother)	Vaginal tissue prolapse
5	16	20.6	G0P0	12	None	None	Vaginal tissue prolapse
6	15	19.3	G0P0	13	Thyroid mass ablation	None	Vaginal bleeding
7	16	22.2	G0P0	11	Thyroid mass ablation	None	Vaginal tissue prolapse
8	38	22.0	G2P1 + 1	16	Caesarean section	None	Vaginal tissue prolapse
9	48	21.1	G3P1 + 2	13	Cholecystectomy	Stomach cancer (father)	Vaginal bleeding[a]
10	46	23.8	G2P1 + 1	14	Caesarean section	Lung cancer (father)	Vaginal bleeding[a]
11	50	21.4	G2P2	16	None	None	Vaginal tissue prolapse
12	49	29.1	G3P2 + 1	19	Appendectomy	None	Abdominal pain and urinary frequency

[a]Two patients were considered to have "cervical polyps" and underwent polypectomy at other hospitals, but the cervical mass recurred soon thereafter; BMI — body mass index

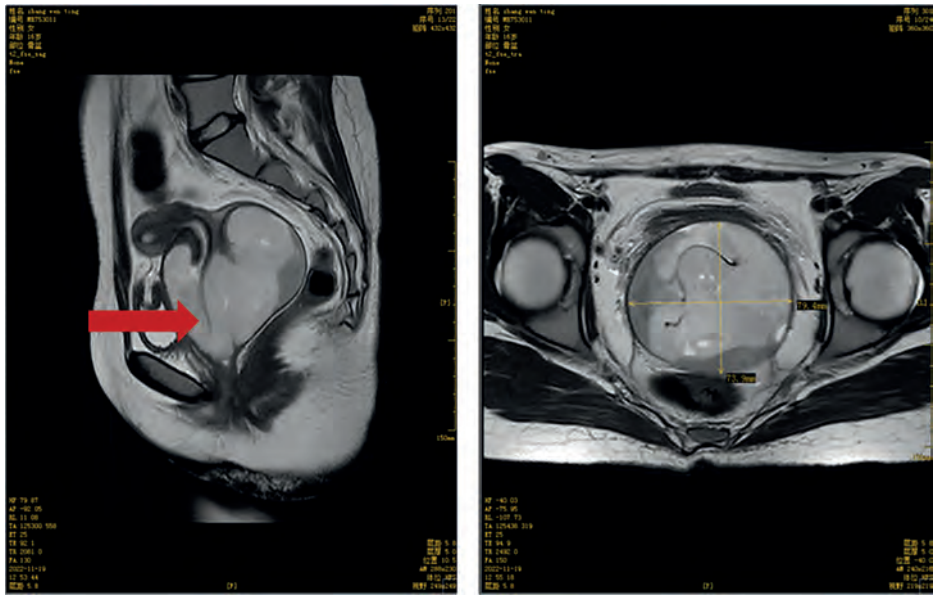


Figure 1. Magnetic resonance images of Patient 6: mixed signal mass in the external cervix and vagina

family requested radical surgery intraoperatively, was diagnosed with cervical malignancy tendency to sarcoma by frozen section during operation. The lesions were found to be significantly reduced in the two patients who were treated with neoadjuvant chemotherapy prior to radical surgery. Four patients underwent conservative surgery. Patient 1 refused radical surgery, and only a lesion biopsy and cervical biopsy were performed. Patients 4, 5 and 7 all underwent cervical mass excision/biopsy first, with postoperative pathology that was considered RMS, and then they accepted cervical conization at our institution. All of them underwent postoperative chemotherapy, but one patient discontinued chemotherapy on her own without receiving a full course (Tab. 3); 2) all five adult patients underwent radical surgery, four received chemotherapies, and one was lost to follow-up.

Prognosis: 1) all 7 adolescent patients were stage I according to the IRSG staging criteria and survived tumour free. The median survival time was 91 months (5 to 213 months). Among 4 patients receiving fertility-sparing management, 1 conceived and delivered successfully (25%). The remaining three patients did not become

Table 2. Pathological features of 12 patients with cervical rhabdomyosarcoma (RMS)

No	Tumour site	The longest tumour diameter [cm]	Immunohistochemistry					Pathological type	Genetic test
			Desmin	Myogenin	MyoD	Myoglobin	Others		
1	Cervix	Unknown	++	–	–	–	/	ERMS (botryoid)	–
2	Cervix	8	++	++	–	Focal+	/	ERMS	–
3	Cervix	9	+	++	+	++	/	ERMS (differentiated with chondrogenesis)	–
4	Cervix	3	Focal+	–	+	/	Vim(+)	ERMS	–
5	Cervix	6	+	+	/		CD56 (+), PCK (focal+)	ERMS + ARMS	No significant heterotopic FOXO1 (FKHR) gene was detected
6	Cervix	11	Focal+	Focal+	+	/	Vim (+), BRG –1 (+)	ERMS[a]	No DICER1 gene mutation was detected
7	Cervix	7.6	+	+	+	+	P53 wild –type expression, caldesmon (focal+), CD10 (+)	ERMS	DICER1 gene mutation was detected
8	Cervix	5.4	/	/	/	/	/	ERMS (botryoid)	–
9	Cervix	3	+	Focal+	+	Focal+	P53 wild-type expression, Vim (+)	ERMS (botryoid)	–
10	Cervix	4	+	Focal+	+	Focal+	P53 wild-type expression	ERMS	–
11	Cervical junction	5.8	+++	Focal+	–	Focal+	SMA (++), caldesmon (++), CD10 (focal+), ER (++)	PRMS (involved vagina)	–
12	Cervix	25	–	+	+	–	/	PRMS (metastasized to the lymph node and omentum)	–

[a]Intraoperative freezing pathology showed a malignant tumour with sarcomatous tendencies; PCK — pan cytokeratin; BRG — BRM/SWI2 related gene; SMA — smooth muscle actin; ERMS — embryonal rhabdomyosarcoma; ARMS — alveolar rhabdomyosarcoma; PRMS — pleomorphic rhabdomyosarcoma

pregnant because they had no immediate pregnancy plans rather than trying and failing to conceive; 2) of the 5 adult patients, 3 had stage I disease, and 2 patients had stage IV disease (all pathological types were PRMS). All patients with PRMS were staged later, as detailed in Table 3. One patient was lost to follow-up. Three patients survived tumour free, and 1 patient with existing pulmonary multiple metastases (IRS stage IV, T2N0M1) at the time of initial diagnosis survived 9 months (as of the follow-up date) with no tumour progression. The median survival time was 21.5 months (9 to 138 months).

DISCUSSION

Aetiology of cervical RMS

The aetiology of cervical RMS is currently unclear. Recent studies have found that RMS, especially ERMS, is more common in children with certain genetic syndromes [5]. These patients often have multiple primary cancers, and a possible correlation between ERMS, especially cervical ERMS, and DICER1 pathogenic variants has been found [6–8]. PAX-FOXO1 fusions are present in approximately 80% of ARMS, and missense mutations in MYOD1 are the most common molecular alterations in adult spindle cell/sclerosing RMS [5]. Of note, three of the cervical RMS patients had either "pneumocyst" or "goiter", and it is unclear whether this was multinodular goiter/pleuropneumoblastoma, which requires a high degree of caution for DICER1 syndrome. In this study, 3 adolescent patients underwent genetic testing, 1 patient with ERMS combined with ARMS had no meaningful FOXO1 (FKHR) gene allele detected, and 2 patients with ERMS who used to have "goiter" who underwent DICER1 genetic testing had a 50% mutation rate (1/2). The genetic susceptibility and molecular driving mechanisms of RMS warrant further investigation.

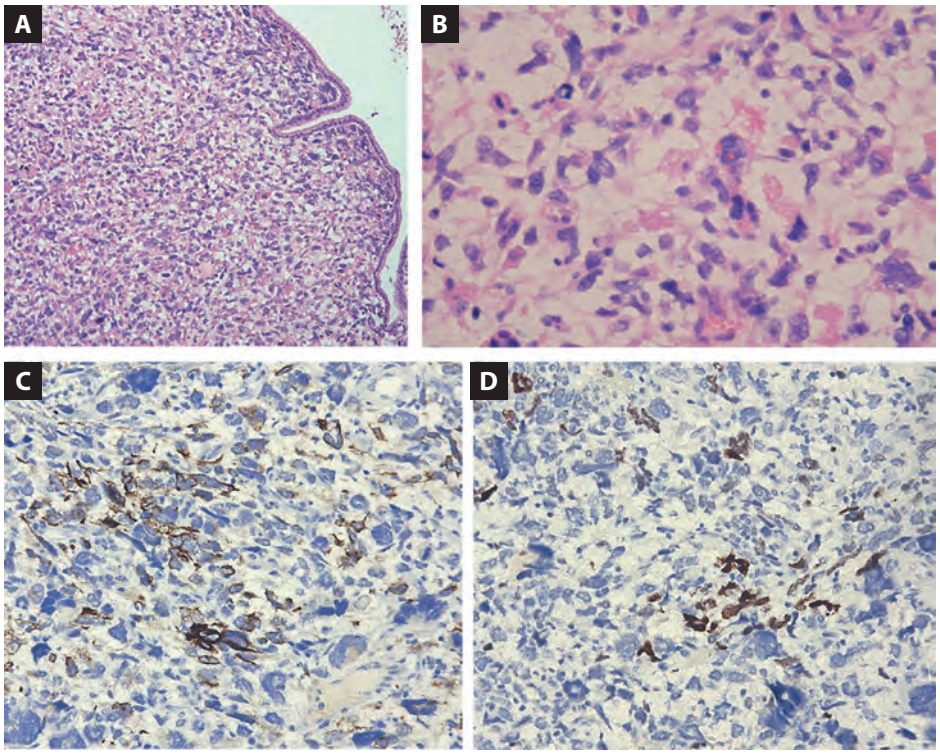


Figure 2. Pathologic characteristics of Patient 6; **A.** The tumour was growing in the cervical stroma (HE stain, ×100); **B.** The tumour cells were round or spindle-shaped, with oval nuclei, empty chromatin, insignificant nucleoli, and occasionally striated myoblasts (HE stain, ×400); **C.** Immunohistochemistry showed that the tumour cells were positive for desmin (×400); **D.** Immunohistochemistry showed the tumour cells to be positive for myoD1 (×400)

Clinical and pathological characteristics of cervical RMS

The median age at diagnosis of primary RMS of the cervix has been reported to be 13.5 years [2]. The median age of gynaecologic RMS in adult women is 32 years, and nearly one-third of patients are diagnosed after the age of 50 years [9]. The ages of the adolescent patients in this study were concentrated between 15 and 17 years, and the ages of the adult patients were between 38 and 50 years, which is generally consistent with previous reports. The clinical presentation of cervical RMS is mainly cervical masses or vaginal bleeding. This study is consistent with previous reports, and one of the patients even had vaginal bleeding leading to severe anaemia (Patient 6, HGB 34 g/L). Because many patients with cervical RMS are children and adolescents and are not sexually active, diagnosis and treatment may be delayed. One patient in this study presented with the initial symptom of abdominal pain and urinary frequency, mainly due to a large mass (25 cm) that partially protruded into the broad ligament and compressed the bladder and ureter. Typical ERMS lesions are nodular, papillary, polypoid, or grape-like masses, which may also grow infiltratively, involve surrounding tissues or metastasize distantly. Due to the relative rarity of cervical RMS, misdiagnosis occurs in up to a quarter of women [1], and cervical ERMS can easily be misdiagnosed as cervical polyps or leiomyosarcoma. In this study, 2 patients were considered for "cervical polyps" to undergo polypectomy in other hospitals, but their cervical mass quickly recurred. Pathologists must improve their understanding of this disease. Careful microscopic observation of RMS can reveal evidence of striated muscle differentiation, with cytoplasmic red staining and transverse fibres. Immunohistochemical staining of MSA, desmin, myoglobin, and myogenin can assist in the differential diagnosis. Microscopically, the tumour cells were round or spindle-shaped, with oval nuclei, empty chromatin, insignificant nucleoli, and occasionally striated myoblasts. Botryoid RMS is a subtype of ERMS characterized by a neoplastic layer that is visible microscopically beneath the intact epithelium [10]. PRMS microscopically shows pleomorphic cells with round, spindle, or polygonal tumour cells. ARMS tumour cells may form glandular vesicle-like or pseudoglandular-like structures and require FISH if necessary. Spindle cell/sclerotic RMS consists of fasciculated spindle cells and has been previously classified as a subtype of ERMS. ERMS is the most common form, occurring in children and adolescents; ARMS is the second most common, occurring mainly in adolescents aged 10–25 years; PRMS is less common, occurring in adults aged 45 years and older, but is highly aggressive; and spindle cell RMS is rare [11]. Most of the patients included in this study had ERMS, and only 2 adult women had PRMS, which is consistent with previous reports. Of note, one 16-year-old

Table 3. Diagnosis, treatment, prognosis and pregnancy outcomes of 12 patients with cervical rhabdomyosarcoma (RMS)

No	Stage (IRSG)	Stage (TNM)	Operative method	Chemotherapy regimen	Survival time [month]	Status at last follow-up	Delivery after treatment
1	I	TXN0M0	Conservative surgery (mass excision)	4 IEP (postoperation)	213	NED	G1P1 (17 years later)
2	I	T2N0M0	Radical surgery (MRH + PPLND + bilateral partial ovariectomy)	4 BEP (before operation); 6 BVP (postoperation)	183	NED	–
3	I	T2N0M0	Radical surgery (RH + PPLND)	2 BEP (before operation); 2 BEP (postoperation); then discontinued chemotherapy on her own	153	NED	–
4	I	T1N0M0	Conservative surgery (cervical conization)[a]	4 VIA (postoperation)	111	NED	No pregnancy plan
5	I	T2N0M0	Conservative surgery (cervical conization)[a]	1 VIA (post mass excision), 1 VIA and 3 vindesine/mycin/ifosfamide (post cervical conization)	91	NED	No pregnancy plan
6	I	T3N0M0	Radical surgery (RH + BS + PPLND)	6 VAC (postoperation)	10	NED	–
7	I	T2N0M0	Conservative surgery (cervical conization)[a]	2 VAC (post mass excision); 2 VAC (post cervical conization)	5	NED	No pregnancy plan
8	I	T2N0M0	Radical surgery (RH + BSO + PPLND)	6 VAC (postoperation)	138	NED	–
9	I	T1N0M0	Radical surgery (RH + BSO + PPLND)	4 VAC (postoperation)	27	NED	–
10	I	T1N0M0	Radical surgery (MRH + BSO + PPLND)	7 VAC (postoperation)	16	NED	–
11	IV[b]	T2N0M1	Radical surgery (TAH + BSO + vaginal partial excision)	4 epirubicin/etoposide/cisplatin (before operation), 3 epirubicin/ifosfamide and 1 ifosfamide (postoperation)	9	Survived without tumour progression	–
12	IV	T4N1M1	Radical surgery (MRH + BSO + PPLND + partial greater omentum excision)	No chemotherapy	Loss to follow-up	Lost to follow-up	–

[a]Cervical mass excision/biopsy was performed with/without chemotherapy before cervical conization; [b]The lung CT prior to initial treatment indicated multiple lung metastases
BEP — bleomycin, etoposide, cisplatin; BS — bilateral salpingectomy; BSO — bilateral salpingo-oophorectomy; BVP — bleomycin, vincristine, cisplatin; IEP — etoposide, cisplatin, ifosfamide; MRH — modified radical hysterectomy; NED — no evidence of disease; PPLND — pelvic/para-aortic lymph node dissection; RH — radical hysterectomy; TAH — total abdominal hysterectomy; VAC — vincristine, actinomycin-D, cyclophosphamide; VIA — vincristine, ifosfamide, actinomycin-D

female patient with ERMS was found to have focal areas containing ARMS components by microscopy, suggesting that multiple different types of RMS can coexist.

Treatment of cervical RMS

Previously, the main surgical approach was considered an extensive hysterectomy with pelvic and para-aortic lymph node dissection. However, patients with cervical RMS are very young, and the inability to have children or even normal development of female sexual characteristics after radical surgery causes great physical and psychological harm to patients. The scope of surgery has now evolved from extensive to limited, and conservative resection has provided adequate local control [2, 8, 12, 13]. The IRSG recommends low-intensity surgical resection combined with chemotherapy to treat uterine RMS [14]. INSTRuCT recommends chemotherapy alone in patients with complete response or organ-sparing surgery in combination with intracavitary brachytherapy (BT) or EBRT; fertility preservation should be considered in all children unless persistent tumours at the corpus uteri require treatment with hysterectomy [2]. Recent international data suggest that only 12% of patients with cervical tumours are treated with radical surgery, and the local control rate is 88% [2]. Surgery (*e.g.*, simple mass excision, polypectomy, cervical conization, radical cervical hysterectomy) to remove the primary tumour and some normal tissues around its periphery for a lesion-free margin should be performed and supplemented by chemotherapy. If complete resection is not possible with initial surgery, cystoscopy, colposcopy, rectal examination under general anaesthesia, and MRI of the abdominopelvic region, if necessary, may be performed

after 3 courses of induction chemotherapy. After 6 courses of treatment, patients need to be re-evaluated. In patients with signs of tumour, local control with excision or radiotherapy is attempted [2]. The specific surgical approach and extent of the procedure will depend on the patient's age, the size of the lesion, the type of tissue, and whether it infiltrates the surrounding organs. However, it should be noted that recurrence after conservative treatment is not uncommon, especially in patients who have not received postoperative chemotherapy or who have had inadequate cycles of chemotherapy [15]. However, most adults with genitourinary RMS have a late diagnosis, extensive lesions, and a high risk of metastasis; most have completed childbirth, in which case more aggressive multimodality therapy, such as radiation and chemotherapy combined with total hysterectomy and local lymph node dissection, is needed [16]. RMS is a chemosensitive tumour. Even in IRSG Group I (localized disease, completely excised, no microscopic residual tumour), postoperative chemotherapy is recommended. In Europe, the standard chemotherapy regimens for RMS are vincristine, ifosfamide, and actinomycin (VIA). The IRSG consensus is to recommend vincristine, actinomycin D, and cyclophosphamide (VAC) [17]. In the IRS-IV study, it was found that VAC, vincristine + ifosfamide + etoposide (VIE), and VIA offered no difference in effectiveness for patients with localized or regional rhabdomyosarcoma. There was no difference in patient outcomes [18]. US researchers chose VAC as the gold standard because cyclophosphamide is less costly and less nephrotoxic [3]. The intensity of chemotherapy was increased in four consecutive trials conducted at IRSG, with detailed protocols available from Arndt CA [19]. The most common toxic side effect was bone marrow suppression, followed by sepsis [18]. Local radiotherapy (brachytherapy) is recommended for patients with limited vaginal or cervical tumours with incomplete response after induction chemotherapy [2]. Experience in the treatment of adults with RMS is limited, and the choice of chemotherapy regimen is usually based on the results of paediatric studies [9]. In the IRS-V trial, the introduction of neoadjuvant chemotherapy was emphasized [4]. Two patients in this study underwent chemotherapy before radical surgery, and the apparent finding of lesion reduction provides additional indirect support for the clinical significance of neoadjuvant chemotherapy. The great variety of treatment regimens received by the patients included in this study was due to the wide age range of patients and the long time span of this study. These results fully reflect the changing philosophy regarding the treatment of cervical RMS during its historical evolution and the principle of individualized treatment. In terms of the choice of surgical modality, all adult patients in this study opted for radical surgery, while more than half of the adolescent patients opted for conservative surgery. In general, in the past, children and adolescents underwent mainly radical surgery, and in the last 10 years, conservative resection was the main operation. However, there are exceptions. For example, in patient 1, only lesion excision and cervical biopsy were performed, and the postoperative chemotherapy regimen was nonclassical and not a full course; however, the patient was followed up for 213 months without recurrence and successfully conceived and delivered spontaneously. In patient 6, the patient was biopsied and then underwent radical surgery, the underlying reasons being a consideration of cervical sarcoma from the intraoperative frozen section and the family members of this patient's subsequent concerns about the disease. This shows that clinicians should both improve their knowledge of cervical RMS to reduce missed diagnoses and misdiagnoses and fully recognize the good prognosis of cervical RMS with reasonable treatment to avoid excessive radical surgery. Adequate doctor–patient communication and description of the disease are also important.

Prognosis of cervical RMS

The National Cancer Database's 5-year overall survival rate for cervical RMS was 66.2% (including adults and children) [20]. The prognoses of children and adolescents and adult patients are different. In children and adolescents, the recently reported 10-year overall survival rate for vaginal and uterine RMS was 92%, and approximately half of the patients did not undergo radical surgery [2, 21]. Researchers in a multicentre study of adult RMS reported a 5-year overall survival rate of 78.2% and a progression-free survival rate of 58.2%, with no patients in the IRS I group dying of the disease [4]. The presence of residual lesions after initial surgery is the most important prognostic factor, and other factors associated with prognosis include disease stage, age, pathological subtype, regional lymph node involvement, whether distant metastases are present, and treatment modality [8, 12]. It is currently believed that polyp-like presentation, embryonal type, and superficial tumours are suitable for preserving reproductive function, and deep infiltrative disease and alveolar/pleomorphic RMS increase the risk of tumour recurrence [17]. The disease-free survival rate in this study was 91% (10/11), which is consistent with recent reports from other countries; patients who survived with tumours and those who were lost to follow-up were all patients with late-stage, adult, PRMS type. Our research shows a good overall prognosis for cervical RMS. Young age, pathological type of ERMS, and early TNM/IRS stage may be predictive of a good prognosis. PRMS is often diagnosed with metastasis, which indicates a poor prognosis.

Pregnancy outcomes of cervical RMS

As mentioned earlier, the current treatment philosophy for ERMS of the genital tract is to protect the patient's reproductive function as much as possible. Successful pregnancy and delivery are the primary goal of fertility-sparing treatment. However, there are fewer reports on pregnancy outcomes after treatment. Piątek S et al. reported a 22-year-old woman diagnosed with RMS of the cervix who had two successful deliveries without disease recurrence [22]. A recent systematic review found that of 35 enrolled patients with cervical ERMS, 3 had a successful pregnancy (3/35, 9%), and their pregnancy rates were lower than those of patients with other uterine sarcomas, such as low-grade endometrial stromal sarcoma (27/63, 43%), adenosarcoma (4/19, 21%), and smooth muscle tumour of uncertain malignant potential (29/84, 35%) [23]. The low pregnancy rates among patients with RMS may be caused by fertility impairment and multidrug chemotherapy, especially high doses of alkylating agents such as cyclophosphamide and ifosfamide [2, 22]. In our study, 4 patients received fertility-sparing treatment, and 1 successfully conceived and delivered (25%). The remaining three patients did not become pregnant because they had no immediate pregnancy plans rather than trying and failing to conceive. The birth rate was higher than that previously reported. This orients our focus towards future reports on the subsequent growth and pregnancy outcomes of other children and adolescents with genital tract RMS.

CONCLUSIONS

In summary, our findings suggest that the treatment of cervical RMS must take patient age and reproductive intent into account. ERMS is the most common subtype of cervical rhabdomyosarcoma in children and adolescent patients, while pleomorphic rhabdomyosarcoma is also common in adults, especially in postmenopausal women. Cervical rhabdomyosarcoma in adult patients, especially postmenopausal women, is often found in the advanced stage, and the prognosis is worse than that of young patients. Cervical rhabdomyosarcoma usually presents with vaginal bleeding and cervical swelling. This tumour occurs mostly in young women, and the families of patients often wish to see a preservation of fertility. In recent years, the treatment philosophy has changed from extensive surgical excision to conservative surgery combined with chemotherapy and radiotherapy for selected patients. The prognosis of this disease has improved significantly, and the pregnancy outcomes are worth anticipating. It is essential to emphasize the importance of chemotherapy in reducing recurrence. However, for patients who have completed childbirth, radical surgery is preferred. Further case reports and systematic evaluations are needed to provide valid data on how to accurately assess patients' conditions, grasp the indications and scope of surgery, and make decisions on chemoradiotherapy regimens.

Article information and declarations

Data availability statement

The clinical and pathological characteristics, treatment approaches and prognosis information will be shared if requested.

Ethics statement

The study was conducted following the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the West China Second University Hospital and informed consent was taken from all the patients.

Author contributions

This manuscript has been read and approved by all authors. All authors contributed to the design of the research. Xiuzhang Yu: concerpt, study design, acquisition of data, analysis and interpretation of data, article draft; Mingrong Qie: analysis and interpretation of data, article draft; Liyan Huang: analysis and interpretation of data, revised article critically; Minmin Hou: concerpt, study design, revised article critically, corresponding author.

Funding

This work was supported by the Key Research and Development Program of Sichuan Province (2022YFS0076).

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Pop CF, Stanciu-Pop CM, Jungels C, et al. Uterine embryonal rhabdomyosarcoma in adult women: a case report on the challenging diagnosis and treatment. Rom J Morphol Embryol. 2023; 64(1): 83–88, doi: 10.47162/RJME.64.1.10, indexed in Pubmed: 37128795.
2. Lautz TB, Martelli H, Fuchs J, et al. INSTRuCT group. Local treatment of rhabdomyosarcoma of the female genital tract: Expert consensus from the Children's Oncology Group, the European Soft-Tissue Sarcoma Group, and the Cooperative Weichteilsarkom Studiengruppe. Pediatr Blood Cancer. 2023; 70(5): e28601, doi: 10.1002/pbc.28601, indexed in Pubmed: 32762004.
3. Jadhav T, Madakshira MG, Garud S. Embryonal rhabdomyosarcoma of the uterine cervix in an adult female. Autops Case Rep. 2023; 13: e2023419, doi: 10.4322/acr.2023.419, indexed in Pubmed: 36777814.
4. Ricciardi E, Plett H, Sangiorgio V, et al. Adult primary cervical rhabdomyosarcomas: A Multicentric cross-national case series. Int J Gynecol Cancer. 2020; 30(1): 21–28, doi: 10.1136/ijgc-2019-000821, indexed in Pubmed: 31780571.
5. Giannikopoulos P, Parham DM. Rhabdomyosarcoma: how advanced molecular methods are shaping the diagnostic and therapeutic paradigm. Pediatr Dev Pathol. 2021; 24(5): 395–404, doi: 10.1177/10935266211013621, indexed in Pubmed: 34107813.
6. Cowan M, Suntum T, Olivas AD, et al. Second primary rhabdomyosarcoma of the uterine cervix presenting with synchronous ovarian Sertoli-Leydig cell tumor: An illustrative case of DICER1 syndrome. Gynecol

Oncol Rep. 2018; 25: 94–97, doi: 10.1016/j.gore.2018.06.008, indexed in Pubmed: 30014022.
7. Apellaniz-Ruiz M, McCluggage WG, Foulkes WD. DICER1-associated embryonal rhabdomyosarcoma and adenosarcoma of the gynecologic tract: Pathology, molecular genetics, and indications for molecular testing. Genes Chromosomes Cancer. 2021; 60(3): 217–233, doi: 10.1002/gcc.22913, indexed in Pubmed: 33135284.
8. Devins KM, Young RH, Ghioni M, et al. Embryonal rhabdomyosarcoma of the uterine cervix: a clinicopathologic study of 94 cases emphasizing issues in differential diagnosis staging, and prognostic factors. Am J Surg Pathol. 2022; 46(11): 1477–1489, doi: 10.1097/PAS.0000000000001933, indexed in Pubmed: 35941719.
9. Elsebaie MAt, Elsayed Z. Is fertility-preservation safe for adult non-metastatic gynecologic rhabdomyosarcoma patients? Systematic review and pooled survival analysis of 137 patients. Arch Gynecol Obstet. 2018; 297(3): 559–572, doi: 10.1007/s00404-017-4591-6, indexed in Pubmed: 29159540.
10. Hermoza AD, de Macêdo Matsushita G, Dos Santos MH, et al. Botryoid embryonal rhabdomyosarcoma of the cervix: A case report. Int J Surg Case Rep. 2023; 102: 107858, doi: 10.1016/j.ijscr.2022.107858, indexed in Pubmed: 36621217.
11. Hollowood K, Fletcher CD. Rhabdomyosarcoma in adults. Semin Diagn Pathol. 1994; 11(1): 47–57, indexed in Pubmed: 8202646.
12. Nasioudis D, Alevizakos M, Chapman-Davis E, et al. Rhabdomyosarcoma of the lower female genital tract: an analysis of 144 cases. Arch Gynecol Obstet. 2017; 296(2): 327–334, doi: 10.1007/s00404-017-4438-1, indexed in Pubmed: 28634755.
13. Terwisscha van Scheltinga S, Rogers T, Smeulders N, et al. Developments in the surgical approach to staging and resection of rhabdomyosarcoma. Cancers (Basel). 2023; 15(2), doi: 10.3390/cancers15020449, indexed in Pubmed: 36672397.
14. Corpron CA, Andrassy RJ, Hays DM, et al. Conservative management of uterine pediatric rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study III and IV pilot. J Pediatr Surg. 1995; 30(7): 942–944, doi: 10.1016/0022-3468(95)90317-8, indexed in Pubmed: 7472949.
15. Imawan DK, Oesman WS, Yuseran H, et al. Recurrent cervical sarcoma botryoides in a 3-year-old female: approach in a limited resource setting. Am J Case Rep. 2019; 20: 838–843, doi: 10.12659/AJCR.915608, indexed in Pubmed: 31197128.
16. Pawlik J, Pawlik W, Branecka-Woźniak D, et al. Rhabdomyosarcoma of the cervix in a post-menopausal woman-an unparalleled phenomenon. Int J Environ Res Public Health. 2021; 18(15), doi: 10.3390/ijerph18157851, indexed in Pubmed: 34360144.
17. Buruiana FE, Gupta B, Singh K. Rhabdomyosarcoma of the cervix in teenagers — Is fertility preservation a feasible option? Gynecol Oncol Rep. 2020; 34: 100677, doi: 10.1016/j.gore.2020.100677, indexed in Pubmed: 33304979.
18. Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. J Clin Oncol. 2001; 19(12): 3091–3102, doi: 10.1200/JCO.2001.19.12.3091, indexed in Pubmed: 11408506.
19. Arndt CS, Donaldson S, Anderson J, et al. What constitutes optimal therapy for patients with rhabdomyosarcoma of the female genital tract? Cancer. 2001; 91(12): 2454–2468, doi: 10.1002/1097-0142(20010615)91:12<2454::aid-cncr1281>3.0.co;2-c.
20. Albert A, Lee A, Allbright R, et al. Primary sarcoma of the cervix: an analysis of patient and tumor characteristics, treatment patterns, and outcomes. J Gynecol Oncol. 2020; 31(3): e25, doi: 10.3802/jgo.2020.31.e25, indexed in Pubmed: 31912680.
21. Minard-Colin V, Walterhouse D, Bisogno G, et al. International Society of Pediatric Oncology Sarcoma Committee, the Children's Oncology Group, the Italian Cooperative Soft Tissue Sarcoma Group, and the European pediatric Soft tissue sarcoma Study Group. Localized vaginal/uterine rhabdomyosarcoma-results of a pooled analysis from four international cooperative groups. Pediatr Blood Cancer. 2018; 65(9): e27096, doi: 10.1002/pbc.27096, indexed in Pubmed: 29781567.
22. Piątek S, Szymusik I, Dańska-Bidzińska A, et al. Fertility-sparing management may be considered in young women with uterine sarcoma. J Clin Med. 2022; 11(16), doi: 10.3390/jcm11164761, indexed in Pubmed: 36012998.
23. Dondi G, Porcu E, De Palma A, et al. Uterine preservation treatments in sarcomas: oncological problems and reproductive results: a systematic review. Cancers (Basel). 2021; 13(22), doi: 10.3390/cancers13225808, indexed in Pubmed: 34830960.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2024, vol 95, no. 9, 460–466

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.96884

Image characteristics and main types of abnormal branching of fetal pulmonary artery in prenatal echocardiography — a retrospective study

Huaying Yan[1], Chunguo Zhang[2], Lihong He[2]

[1]Department of Ultrasound, Hospital of Chengdu University of Traditional Chinese Medicine, Jinniu District, Chengdu, China
[2]Department of Ultrasound, Sichuan Provincial Maternity and Child Health Care Hospital, Chengdu, Sichuan, China

ABSTRACT

Objectives: To explore the image characteristics and main types of abnormal branching of fetal pulmonary artery in prenatal echocardiography.

Material and methods: A retrospective analysis of 41 cases diagnosed with abnormal branching of fetal pulmonary artery by prenatal echocardiography was made. The image characteristics of the abnormalities, their combination with intra- or extra-cardiac malformations and chromosomal anomalies were analyzed.

Results: The results of prenatal echocardiography showed that, among the 41 cases: 1) 4 cases were with anomalous origin of single pulmonary artery, 8 cases with pulmonary artery agenesis, 9 cases with pulmonary artery sling; 20 cases with crossed pulmonary arteries; 2) 11 cases were complicated with intracardiac malformations and 10 with extracardiac malformations; 3) only 7 case underwent chromosomal examination and 1 tested abnormal; 4) pregnancy outcomes: 25 fetuses were born and their abnormalities confirmed by echocardiography (MRI or surgery) to be consistent with prenatal ultrasound diagnosis; 16 cases had their pregnancy terminated due to their combination with other severe malformations, which were confirmed by pathological anatomy after induced abortion.

Conclusions: Prenatal echocardiography can provide detailed images for the diagnosis of abnormal branching of fetal pulmonary artery, which can be complicated by intra- and extracardiac malformations and chromosomal anomalies and should be alerted.

Keywords: prenatal diagnosis; echocardiography; abnormal branching of pulmonary artery

Ginekologia Polska 2024; 95, 6: 460–466

INTRODUCTION

The prevalence of abnormal branching of pulmonary artery is about 1.2 ‰ to 3 ‰ [1], which can be inherited in an autosomal dominant, autosomal recessive, or X-linked pattern, and are often combined with intra- or extracardiac abnormalities. Abnormal branching of pulmonary artery generally includes abnormal origin of single pulmonary artery, unilateral pulmonary artery agenesis (UPAA), pulmonary artery sling, crossed pulmonary arteries (CPAs), *etc.* and for the diagnosis of which prenatal echocardiography is the first choice. This study retrospectively analyzed the images of 41 abnormal branching of fetal pulmonary artery diagnosed by prenatal echocardiography, their combination with intra- or extracardiac malformations, and associated chromosomal anomalies, which are reported as follows.

MATERIAL AND METHODS

General data

41 fetuses with the diagnosis of abnormal branching of pulmonary artery by prenatal echocardiography at the Hospital of Chengdu University of Traditional Chinese Medicine and Sichuan Provincial Maternity and Child Health Care Hospital from January 2014 to December 2020 were retrospectively studied. The mothers aged between 20–40 years, with a mean age of (30 ± 10) years. The gestational age ranged between 20–34 weeks, with a mean of (27 ± 7) weeks. The inclusion criteria were pregnant women in good health, with no special past or family history, and who underwent routine prenatal ultrasound examination of the fetus between 22 to 32 weeks of pregnancy in two hospitals. Abnormal branching of fetal pulmonary artery in prenatal echocardiography.

Corresponding author:
Huaying Yan
Department of Ultrasound, Hospital of Chengdu University of Traditional Chinese Medicine, No. 39, 12 Qiao Road, Jinniu District, 610075 Chengdou, China
e-mail: yanhuaying1983@163.com

Received: 8.08.2023 Accepted: 10.12.2023 Early publication date: 19.01.2024

The exclusion criteria were pregnant women who should not be originally suitable for pregnancy, but became pregnant. The excluded pregnant women are those with severe conditions including congenital heart disease and other diseases such as severe hyperthyroidism that would put the mother in grave danger, or with abdominal wall fat hypertrophy causing poor fetal image quality.

Apparatus and methods

Color Doppler ultrasound including GE Voluson E8, Samsung WS80A, Philips EPIQ 7 and Mindray Resona8S were used to perform a comprehensive screening of the fetus using a transabdominal probe (probe frequency 1–8 MHz). If evidence of abnormal branching of pulmonary artery were observed on the three-vessel and tracheal view or the three-finger view, a further inspection for signs of other intra- or extra-cardiac anomalies was conducted. All cases were engaged in follow-ups. This study followed standard medical ethics principles.

Observation

The image characteristics of abnormal branching of pulmonary artery on sections of the three-vessel and tracheal view or the three-finger view were observed, the condition's combination with intra- or extra-cardiac anomalies, and chromosomal anomalies investigated.

RESULTS

Image characteristics of abnormal branching of fetal pulmonary artery, their combination with intra- or extra-cardiac malformations, and chromosomal anomalies

Findings on the three-finger view

Normally ductus arteriosus, left pulmonary artery (LPA) and right pulmonary artery (RPA) can be seen from left to right on this view (Fig. 1).

Of the 41 fetuses studied, there were:4 cases of anomalous origin of single pulmonary artery: 1 case with the LPA originating from the aortic arch (Fig. 2); 3 cases with the RPA originating from the ascending aorta (Fig. 3).

Eight cases with UPAA: 2 on the left and 6 on the right (Fig. 4).

Nine cases with pulmonary artery sling: 8 cases in the entire form (the LPA originated posterior to the RPA, passed between the trachea and esophagus, bypassed the right main bronchus and distal trachea, and traveled towards the left pulmonary hilar, as shown in Fig. 5) and 1 in a partial form (the left inferior and right pulmonary arteries originated from the MPA, the left upper pulmonary artery originated from the RPA, as shown in Fig. 6).

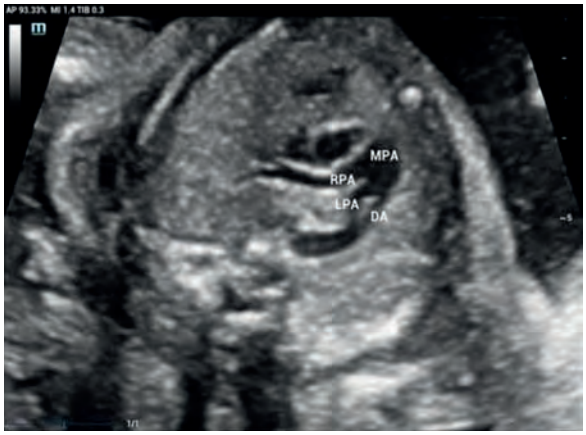


Figure 1. The normal three-finger view. Normally ductus arteriosus, left pulmonary artery (LPA) and right pulmonary artery (RPA) can be seen from left to right on this view; DA — ductus arteriosus; MPA — main pulmonary artery

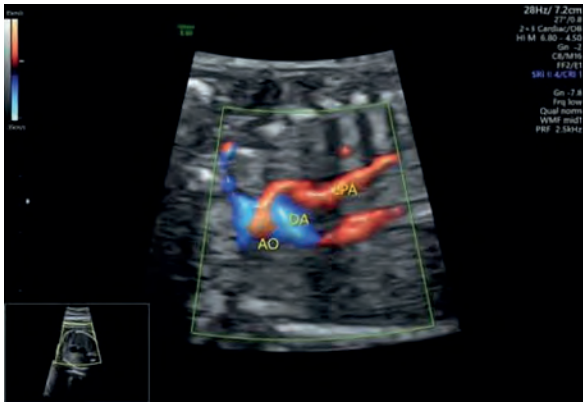


Figure 2. Left pulmonary artery (LPA) originates from the aortic arch; AO — aorta; DA — ductus arteriosus

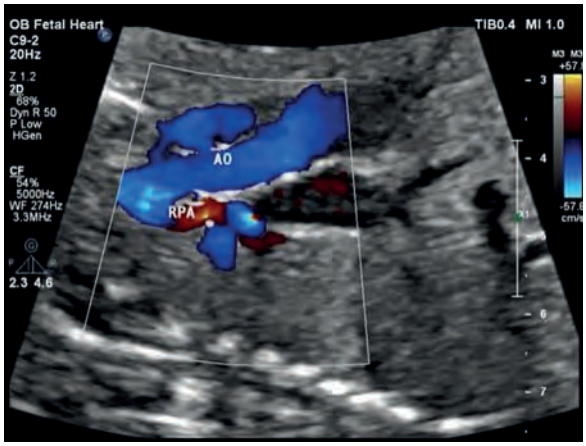


Figure 3. Right pulmonary artery (RPA) originates from the ascending aorta; AO — aorta

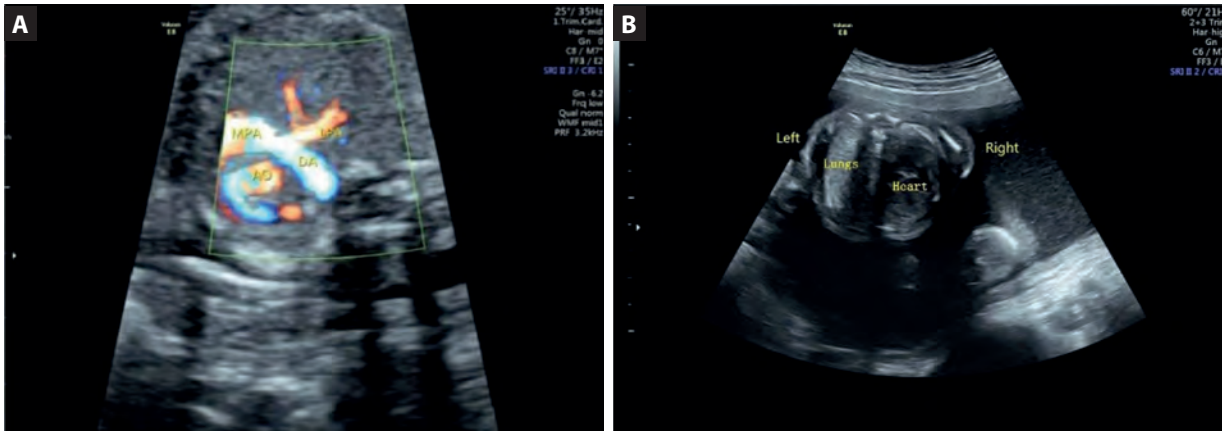


Figure 4. Right pulmonary artery (RPA) agenesis; **A.** Right pulmonary artery is not seen in the bifurcation section of the pulmonary artery; **B.** Right lung is not seen in the right chest cavity, dextral heart (the heart is located in the right chest cavity, the apex of the heart points to the right); AO — aorta; DA — ductus arteriosus; MPA — main pulmonary artery; LPA — left pulmonary artery

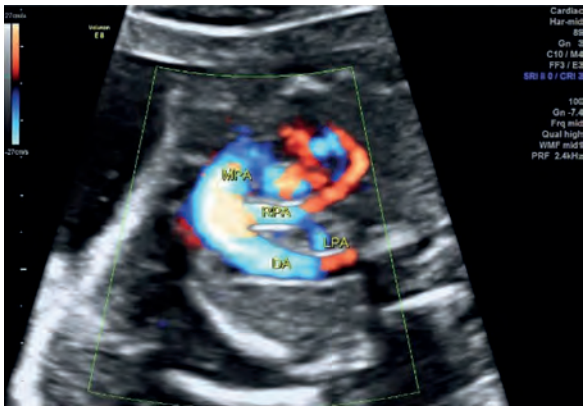


Figure 5. Pulmonary artery sling in an entire form. The left pulmonary artery (LPA) originated posterior to the right pulmonary artery (RPA), passed between the trachea and esophagus, bypassed the right main bronchus and distal trachea, and traveled towards the left pulmonary hilar; MPA — main pulmonary artery; DA — ductus arteriosus

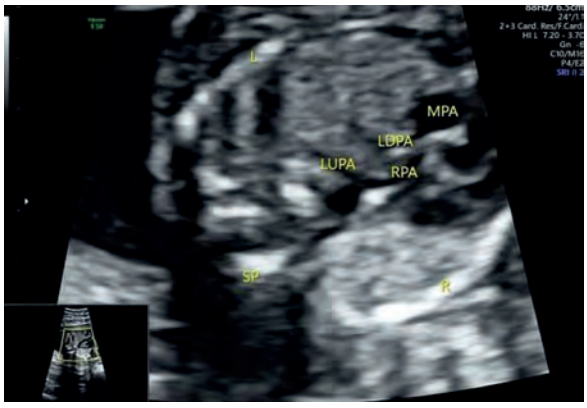


Figure 6. Pulmonary artery sling in a partial form. The left inferior and right pulmonary arteries (RPA) originated from the main pulmonary artery (MPA), the left upper pulmonary artery originated from the RPA; LUPA — left upper pulmonary artery; LDPA — left lower pulmonary artery; L — left; R — right; SP — spine

Twenty cases with crossed pulmonary arteries (CPAs): the LPA originated from the right wall of the MPA and traveled towards the left to the left lung, and the RPA originated from the left wall of the MPA and traveled towards the right to the right lung, with the LPA and RPA crossing at their beginnings (Fig. 7).

Abnormal branching of fetal pulmonary artery and their combination with intra- or extracardiac malformations

Eleven of the 41 cases were combined with intracardiac malformations (2 with anomalous origin of single pulmonary artery, 1 with UPAA, 5 with pulmonary artery sling, and 3 with CPAs).

Ten of the 41 cases were combined with extracardiac malformations (1 with anomalous origin of single pulmonary artery, 8 with UPAA, and 1 with pulmonary artery sling).

Chromosomal findings

Only 7 of the 41 fetuses were examined for chromosomes (1 case with the RPA originating from the ascending aorta, 2 cases with pulmonary artery sling and 4 cases with CPAs), of which 1 case had chromosomal anomalies (the case of CPAs: deletion of chromosome 22).

Pregnancy outcomes

Twenty-five fetuses were born, and their prenatal diagnoses were confirmed by echocardiography (MRI or surgery); 16 pregnancies were terminated due to their combination with other severe anomalies, which were confirmed by pathological anatomy after induced abortion (Tab. 1).

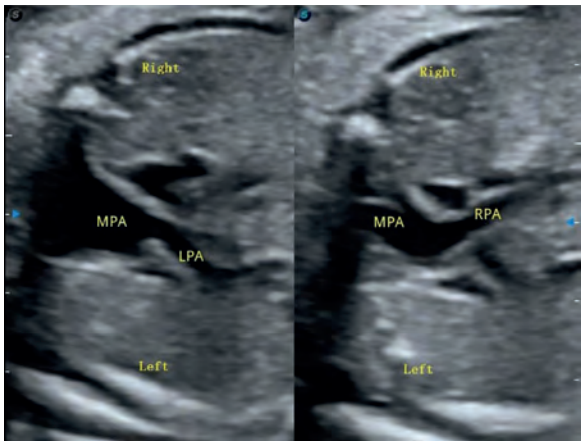


Figure 7. Crossed pulmonary arteries (CPAs); The left pulmonary artery (LPA) originated from the right wall of the main pulmonary artery (MPA) and traveled towards the left to the left lung, and the right pulmonary arteries (RPA) originated from the left wall of the MPA and traveled towards the right to the right lung, with the LPA and RPA crossing at their beginnings

DISCUSSION

Anomalous origin of unilateral pulmonary artery

It was found in the cases that pulmonary artery on one side normally originated from the MPA and pulmonary artery the other side anomalously originated from the aorta, ductus arteriosus or other sites, a condition that was suspected to be associated with abnormal embryonic development. The occurrence of unilateral pulmonary artery originating from the aorta is due to delayed migration of the sixth aortic arch on the affected side to the opposite side during embryonic stage and rest on the arterial side of the aortic sac, eventually leading to the origin of the affected pulmonary artery from the proximal aorta or other sites, with single pulmonary artery originating from the aortic arch or ascending aorta more commonly seen. Previous studies reported cases such as aberrant right pulmonary artery that originated from the right ductus arteriosus emanating from the brachiocephalic trunk [2], anomalous origin

Table 1. Profile of 41 cases with abnormal branching of fetal pulmonary artery

Type	No.	Intracardiac malformations	Extracardiac malformations	Outcome
Anomalous origin				
LPA originating from the aortic arch	1	None	None	Induction
RPA originating from the ascending aorta	1	None	None	Induction
	2	Coarctation of the aorta	None	Induction
	3	VSD, tricuspid atresia, pulmonary atresia	Visceral inversion, right isomerism	Induction
UPAA				
On the left	1	None	Absent left lung, intestinal atresia	Induction
	2	None	Absent left lung	Induction
On the right	1–5	None	Absent right lung	Induction
	6	dextroversion	Absent right lung, dysplasia of thoracic vertebrae	Induction
PA sling				
In the entire form	1–4	None	None	Born
	5	Tetralogy of Fallot	None	Induction
	6	PLSVC	None	Born
	7	Coarctation of the aorta, PLSVC	None	Born
	8	VSD, coarctation of the aorta, pulmonary valve stenosis, PFAA	None	Induction
In a partial form	1	VSD, pulmonary valve stenosis, ARSA, dextrocardia	Cleft lip and cleft palate, microtia of the right ear	Induction
CPAs				
	1	DORV, pulmonary valve stenosis	None	Induction
	2	ARSA	None	Born
	3–19	None	None	Born
	20	VSD	None	Born

LPA — left pulmonary artery; RPA — right pulmonary artery; VSD — ventricular septal defect; UPAA — unilateral pulmonary artery agenesis; PLSVC — persistent left superior vena cava; PFAA — persistent fifth aortic arch; ARSA — aberrant right subclavian artery; CPAs — crossed pulmonary arteries; DORV — double outlet right ventricle

of the LPA from the left ductus arteriosus emanating from the brachiocephalic trunk [3] or from the innominate artery [4]. The anomalous origin of a unilateral pulmonary artery from the ductus arteriosus was not found in this study. The reason might be the limited sample size and more samples shall be included in future studies. The anomalous origin of the pulmonary artery may exist alone or be complicated with other malformations, among which pulmonary atresia with ventricular septal defect (VSD) and pulmonary artery stenosis are the most common [5]. The anomalous origin of the RPA is often combined with aortopulmonary *window* (AP *window*), aortic arch dissection [6, 7], pulmonary aneurysm, pulmonary hypertension or heart failure [8]. In this study, for case with RPA originating from the ascending aorta, one case was combined with coarctation of the aorta, another one combined with VSD, tricuspid atresia, pulmonary valve atresia, visceral inversion and right isomerism, and the rest were not found to have been combined with other malformations. Studies have reported [9] that patients with anomalous origin of unilateral pulmonary artery from the ascending aorta might have a microdeletion of 22q11. In this study only one case underwent chromosomal examination, and the result was normal, therefore the correlation between anomalous origin of unilateral pulmonary artery and chromosomal anomalies could not be established yet.

Unilateral pulmonary artery agenesis (UPAA)

Normally during the embryonic period, the pulmonary artery trunk originates from the aortic sac, the distal MPA and the proximal pulmonary artery are formed by the sixth aortic arch, and the distal pulmonary artery develops into the pulmonary vascular plexus. In UPAA cases, the proximal sixth aortic arch would degenerate, the internal pulmonary artery would be persistently connected to the distal sixth aortic arch, a situation arises from which the pulmonary blood supply on the affected side would come from branches of the aberrant artery while the bronchial artery would originate from the descending aorta or the innominate artery, thus creating an aortopulmonary collateral circulation. In a fetus with UPAA combined with tetralogy of Fallot, the distal end of the existing single pulmonary artery is connected to the aortic arch via the ductus arteriosus. After birth, poor blood supply and collateral circulation from the aortic branches on the affected side would result in local ischemia and hypoxia, which in turn lead to vasoconstriction, hyperplasia, stenosis, increased pulmonary vascular resistance and eventually pulmonary hypertension [10]. Right pulmonary artery agenesis is often combined with coarctation of the aorta [11], left pulmonary artery agenesis is often associated with a right-sided aortic arch [12], and pulmonary artery agenesis or dysplasia is often combined with right isomerism [13]. In this study, all cases of pulmonary artery agenesis were combined with pulmonary agenesis, including one case of right pulmonary artery agenesis combined with dextroversion and thoracic spine dysplasia; and one case of left pulmonary artery agenesis combined with intestinal atresia. Right pulmonary artery agenesis was found to be more frequent than left pulmonary artery agenesis, which is inconsistent with previous reports [14]. Right pulmonary artery agenesis was often associated with DiGeorge's syndrome [15]. All the eight cases of pulmonary artery agenesis in this study were not examined for chromosomes, and the relationship between pulmonary artery agenesis and chromosomal anomalies still needs to be explored.

Pulmonary artery sling

Normally, in the early embryonic stage, the left and right pulmonary arteries would emanate from both sides of the lung bud and connect to the sixth pair of aortic arches on both sides as the embryo develops. If the LPA failed to connect to the sixth arch on the left side, it would originate from the RPA, then pulmonary artery sling, also called aberrant left pulmonary artery, would occur. This anomaly can be present in an entire form or a partial form. In an entire form both LPAs originates from the RPA, while in a partial form either of the two LPAs originates from the RPA with the aberrant LPA passes through the trachea and the esophagus, resulting in a vascular ring and frequent compression of the lower trachea, the right main bronchus and the esophagus. Since the airway hasn't started its function during the fetal period, no relevant clinical symptoms would present. After birth, compression of the airway by the aberrant LPA may cause respiratory disturbances and recurrent respiratory infections in newborns; compression of the esophagus may cause swallowing disorders. In this study, there was one case of partial pulmonary sling: the left inferior PA and the RPA originated from the MPA, and the left superior PA originated from the RPA, a type that is rare [16]. Previous studies reported that pulmonary artery slings would often be combined with intra- or extracardiac malformations [17–19]. In this study, 55.5% (5/9) of the cases were combined with intracardiac malformations, mainly tetralogy of Fallot, VSD and permanent left superior vena cava (PLSVC), and only one case was combined cleft lip and cleft palate and right microtia, while the remaining cases did not have combined extracardiac malformations. Studies have reported [20, 21] that fetal pulmonary artery sling is often combined with chromosomal anomalies. In this study, chromosomal examination was performed for two cases and both results were normal. The current inadequate literature on this anomaly and the small sample yet cannot provide convincing explanations on the correlation between pulmonary artery sling and chromosomal anomalies.

Crossed pulmonary arteries (CPAs)

In this condition, both the left PA and right PA originate from the MPA and cross each other at their beginnings in front of the trachea and then travel to the right and left respectively. Despite the change in their spatial relationship, their course between the cross and the hila are normal. The cross would not result in any mechanical airway obstruction or hemodynamic abnormalities. It has been reported [22] that CPAs might be associated with abnormal differentiation of the MPA during embryonic development, resulting in a counterclockwise rotation at the MPA bifurcation. CPAs may occur alone or in combination with other intra- or extracardiac malformations and chromosomal anomalies. Studies have reported [23] that CPAs is susceptible to the combination of conotruncal defects and genetic syndromes, including VSD and double outlet right ventricle (DORV), and is associated with trisomy 18 and 22q11 deletion. In this study, 3 of the 19 CPAs cases were combined with intracardiac malformations: one with DORV and pulmonary valve stenosis, one with aberrant right subclavian artery (ARSA), and one with VSD; 4 of the 19 cases had chromosomal examinations, and one of them was found to have chromosome 22 deletion, with a 2.54 Mb deletion in the region of 22q11.21, demonstrating that CPAs would be combined with chromosomal anomalies. Chromosomal examination should be routinely performed when such abnormalities are encountered.

The treatment and follow-up results after birth

Follow-ups among the 25 newborns, 6 had pulmonary artery sling (Tab. 1, No. 1–4 without malformations, No. 6 with PLSVC, and No. 7 with aorta coarctation and PLSVC) and within one year after birth all received surgeries of pulmonary artery sling to correct the condition. Their follow-ups showed satisfactory patient outcomes. The other 19 cases had crossed pulmonary arteries (Tab. 1, No. 2 with ARSA, No. 3–19 without malformations, No. 20 with VSD). Case No. 2 didn't receive any surgeries for the aberrant right subclavian artery after birth and the follow-up found no signs of dyspnea or dysphagia for the patient. Cases No. 3–19 didn't receive any surgeries after birth and the follow-ups showed good results. Case No. 20 received VSD transcatheter repair at the age of 2 and the follow-ups showed satisfactory patient outcome. The follow-ups were conducted mainly through telemedicine communications or on-site visits.

Limitations

In this study, only seven cases underwent chromosomal examination. The sample was small and cannot provide adequate evidence to elucidate in detail the correlation between the abnormal connection of pulmonary artery branches and chromosomal anomalies. The small portion of the cases screened with malformations to have further chromosomal and microarray examinations is mainly due to the socioeconomic factors. As society advances and the patient education improve, we hope more affected cases could have genetic consultations and chromosomal and microarray examinations. Investigations with larger samples and involving wider regions are required to cast light on the genetic changes of this anomaly.

CONCLUSIONS

In conclusion, prenatal echocardiography can clearly show that the image characteristics and the main types of abnormal branching of fetal pulmonary artery and the associated intra- or extracardiac malformations. The pregnancy of fetus who have anomalous origin of single pulmonary artery and unilateral pulmonary artery agenesis combined with severe deformity of pulmonary artery sling or crossed pulmonary arteries should be terminated while the pregnancy of fetuses with pulmonary artery sling or crossed pulmonary arteries without severe malformations can be born and closely followed up. Our results can provide a more comprehensive information for prenatal consultation and eugenics.

Article information and declarations

Data availability statement

All data generated or analyzed during this study are included in this published article. The data of this study is available upon request.

Ethics statement

This study protocol was reviewed and approved by the Ethics Committee of the hospital of Sichuan Provincial Maternity and Child Health Care Audit Committee, Written informed consent was obtained from participants prior to the study.

Authors contributions

HYY conceived the study and literature review and drafted the manuscript. CGZ analyzed the data and interpreted data. LHH revised the manuscript and supervised the whole study. All authors read and approved the final manuscript.

Funding

None.

Acknowledgements

None.

Conflict of interest

All the authors declare no conflicts of interest.

Supplementary material

None.

REFERENCES

1. Hirsig LE, Sharma PG, Verma N, et al. Congenital Pulmonary Artery Anomalies: A Review and Approach to Classification. J Clin Imaging Sci. 2018; 8: 29, doi: 10.4103/jcis.JCIS_9_18, indexed in Pubmed: 30147993.
2. Han J, Yu S, Hao X, et al. Prenatal Diagnosis of Bilateral Ductus Arteriosi and an Anomalous Origin of the Right Pulmonary Artery From the Right-Sided Duct. J Ultrasound Med. 2018; 37(12): 2961–2962, doi: 10.1002/jum.14655, indexed in Pubmed: 29689596.
3. Chen L, Xu H, Zhou L, et al. Prenatal diagnosis of ductal origin of distal pulmonary artery: presentation of three cases and literature review. Ultrasound Obstet Gynecol. 2022; 60(2): 284–290, doi: 10.1002/uog.24799, indexed in Pubmed: 34687572.
4. Karmegaraj B, Vaidyanathan B. Right aortic arch, bilateral ductus arteriosus, and anomalous origin of left pulmonary artery from innominate artery in a fetus with normal intracardiac anatomy. Echocardiography. 2020; 37(5): 796–798, doi: 10.1111/echo.14668, indexed in Pubmed: 32324931.
5. Li X, Mu Z, Li Xu, et al. Prenatal diagnosis of anomalous origin of pulmonary artery. Prenat Diagn. 2018; 38(5): 310–317, doi: 10.1002/pd.5235, indexed in Pubmed: 29451683.
6. Binsalamah ZM, Greenleaf CE, Heinle JS. Type A interrupted aortic arch and type III aortopulmonary window with anomalous origin of the right pulmonary artery from the aorta. J Card Surg. 2018; 33(6): 344–347, doi: 10.1111/jocs.13717, indexed in Pubmed: 29749109.
7. Dönmez YN, Aykan HH, Peker RO, et al. Association of interrupted aortic arch, aortopulmonary window with anomalous origin of the right pulmonary artery from the aorta, one-stage repair and postoperative outcomes: A case report. Anatol J Cardiol. 2021; 25(6): 447–450, doi: 10.14744/AnatolJCardiol.2020.48465, indexed in Pubmed: 34100732.
8. Musab Hamoud A, Mshari Fahad A, Atheer Abdullah A, et al. Late diagnosis of anomalous right pulmonary artery originated from ascending aorta: Associated with small pulmonary artery aneurysm. Radiol Case Rep. 2020; 15(11): 2294–2302, doi: 10.1016/j.radcr.2020.08.068, indexed in Pubmed: 32983303.
9. Garg P, Talwar S, Kothari SS, et al. The anomalous origin of the branch pulmonary artery from the ascending aorta. Interact Cardiovasc Thorac Surg. 2012; 15(1): 86–92, doi: 10.1093/icvts/ivs110, indexed in Pubmed: 22467006.
10. Seedat F, Kalla IS, Feldman C. Unilateral absent pulmonary artery in an adult - A diagnostic and therapeutic challenge. Respir Med Case Rep. 2017; 22: 238–242, doi: 10.1016/j.rmcr.2017.09.004, indexed in Pubmed: 28951831.
11. Wang Yu, Zhang J, Feng W, et al. Absence of the fetal right pulmonary artery complicated with coarctation of the aorta: Prenatal and postnatal diagnosis. Echocardiography. 2019; 36(9): 1787–1789, doi: 10.1111/echo.14470, indexed in Pubmed: 31487058.
12. Wenxiu Li, Yuan Z, Chaoning H, et al. Prenatal diagnosis of anomalous origin of one pulmonary artery branch by two-dimensional echocardiography: summary of 12 cases. Cardiol Young. 2020; 30(1): 39–46, doi: 10.1017/S1047951119002890, indexed in Pubmed: 31845638.
13. Pan JY, Lin CC, Chang JP. Fontan Operation in a Patient with Severe Hypoplastic Right Pulmonary Artery, Single Ventricle, and Heterotaxy Syndrome. Acta Cardiol Sin. 2016; 32(5): 612–615, doi: 10.6515/acs20160105a, indexed in Pubmed: 27713611.
14. Tian M, Zheng M. Unilateral absence of pulmonary artery analysis based on echocardiographic feature. Rev Cardiovasc Med. 2021; 22(2): 483–488, doi: 10.31083/j.rcm2202055, indexed in Pubmed: 34258916.
15. Garg A, Azad S, Radhakrishnan S. Isolated absent right pulmonary artery in an infant with 22q11 deletion. Cardiol Young. 2021; 31(11): 1850–1852, doi: 10.1017/S1047951121001487, indexed in Pubmed: 33879276.
16. Wang G, Zhou G. Left superior pulmonary artery sling. J Card Surg. 2019; 34(12): 1659–1660, doi: 10.1111/jocs.14268, indexed in Pubmed: 31557345.
17. Muthialu N, Martens T, Kanakis M, et al. Repair of pulmonary artery sling with tracheal and intracardiac defects. Asian Cardiovasc Thorac Ann. 2020; 28(8): 463–469, doi: 10.1177/0218492320943342, indexed in Pubmed: 32659103.
18. Tedla B, Golding F, Ryan J, et al. Fetal Diagnosis of Dextroposition, Left Pulmonary Artery Sling, Partial Anomalous Left Pulmonary Artery, and Aortic Coarctation. CASE (Phila). 2022; 6(3): 114–118, doi: 10.1016/j.case.2022.01.007, indexed in Pubmed: 35602990.
19. Matsumoto Y, Kamada M, Nakagawa N, et al. Double vascular ring: a case report of double aortic arch and concurrent pulmonary artery sling. Eur Heart J Case Rep. 2019; 3(2), doi: 10.1093/ehjcr/ytz036, indexed in Pubmed: 31449592.
20. El Batti S, Ben Abdallah I, Julia P, et al. Crossed pulmonary arteries as additional cause of dysphagia in association with right aortic arch and Kommerell diverticulum. Surg Radiol Anat. 2018; 40(10): 1165–1168, doi: 10.1007/s00276-018-2085-2, indexed in Pubmed: 30128895.
21. Delogu AB, Mariani F, Graziani F, et al. Pulmonary artery sling in a 22-month-old boy with 18q deletion syndrome: A rare but possible association. Echocardiography. 2022; 39(5): 741–744, doi: 10.1111/echo.15349, indexed in Pubmed: 35434845.
22. Xiong Y, Gan HJ, Liu T, et al. Prenatal diagnosis of crossed pulmonary arteries. Ultrasound Obstet Gynecol. 2010; 36(6): 776–777, doi: 10.1002/uog.8828, indexed in Pubmed: 20812378.
23. Raza R, Khandwala K, Qayyum H, et al. A Variant of Crossed Pulmonary Arteries in Association with Coarctation of Aorta. Cureus. 2018; 10(4): e2477, doi: 10.7759/cureus.2477, indexed in Pubmed: 29904618.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2024, vol. 95, no. 6, 467–472

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/gpl.96837

Clinical correlation and prognostic value of xanthine and inflammatory factors in postpartum depression

Lizhen Zhang[1], Bo Zhou[1], Peter Wang[2], Lilu Shu[2]

[1]Ningxiang People Hospital, Ningxiang, China
[2]Zhejiang Zhongwei Medical Research Center, Hangzhou, China

ABSTRACT

Objectives: As a common postpartum complication, postpartum depression is an important social and health problem. Postpartum depression causes many changes in relevant indicators, such as inflammatory factors and thyroid hormones. However, the effects of inflammatory factors, thyroid hormones and xanthine on postpartum depression have not yet been fully elucidated. Therefore, it is of great clinical significance to clarify the changes in the key indicators of postpartum depression.

Material and methods: A total of 139 pregnant women were included in this study. Finally, only 56 patients completed the Edinburgh Depression Scale (EPDS) evaluation and blood sample collection.

Results: In the current study, 34 (60.7%) patients were normal, 10 (17.9%) women were depressive tendency and 12 (21.4%) women developed depression. Among the serum indexes detected, the expression levels of thyroid function indexes T3, T4 and TSH, and inflammatory factors, such as hs-CRP, IL-1β, IL-6 and TNF-α, in the EPDS ≥ 9 group were slightly higher than those in the normal group (EPDS < 9). Xanthine levels in the depression group (EPDS ≥ 13) were significantly higher than normal group (EPDS < 9).

Conclusions: Our findings suggest that xanthine levels in patients with postpartum depression were increased significantly, but there were no significant changes in thyroid function and some inflammatory indexes. Therefore, timely detection and intervention of maternal xanthine may help reduce the incidence of postpartum depression.

Keywords: postpartum depression; EDS; thyroid function; inflammatory factors; xanthine; IL-6; EPDS

Ginekologia Polska 2024; 95, 6: 467–472

INTRODUCTION

Depression is a disease that affects the body, mood and thinking in human [1]. It can also affect eating and sleeping rules, people feelings and ways of thinking [2]. For women, pregnancy not only produces physiological changes in various systems, but also leads to corresponding psychological changes, which often leads to mental disorders, especially depression [3]. Postpartum depression is a common postpartum complication, which is mainly manifested in maternal irritability, fear, timidity, emotional instability, uneasiness, anxiety, depression and excessive concern about their own and infant health during the puerperium [4, 5]. It usually starts within two weeks after giving birth and gradually worsens. It is obvious at 4 ~ 6 weeks after birth and can recover by itself within 3 ~ 6 months, but some parturients can last for 1~2 years [6]. The incidence rate of postpartum depression is approximately 10%~18% and has been increasing year by year. The incidence of postpartum depression in the second child is 1.5 times higher than that in the first child [7, 8]. The occurrence of postpartum depression seriously affects the physical and mental health of pregnant women and is not conducive to the growth and development of newborns. It is an urgent problem to be concerned and should be solved by the society at present.

Many studies have shown that postpartum depression is related to inflammatory response [9]. The inflammatory factors often include IL-6, hs-CRP, TNF-a and IL-1b [10, 11]. The pregnancy process is an noninflammatory state, showing an increase in pro-inflammatory factors in the third trimester of pregnancy [12]. Dowlati et al. [13] found that patients with major depression had higher levels of TNF-α and IL-6 than patients without depression. In recent studies on perinatal

Corresponding author:
Peter Wang or Lilu Shu
Zhejiang Zhongwei Medical Research Center, No. 452, Sixth Street, 310018 Hangzhou, China
e-mail: wangpeter2@hotmail.com; or shulilu12345@126.com

Received: 04.08.2023 Accepted: 19.11.2023 Early publication date: 16.01.2024

depression, it was found that pro-inflammatory biomarkers IL-6, IL-1β, TNF-α and CRP were associated with depressive symptoms, anxiety and mood disorders [14–16]. However, the effects of inflammatory factors on postpartum depression are quite different, suggesting that it needs to be further clarified [17]. Studies have also revealed that changes in thyroid hormones can lead to postpartum depression [18, 19]. The homeostasis of thyroid hormones during pregnancy is challenged due to adaptive changes in the hypothalami pituitary thyroid (HPT) axis [20]. In addition, the increase of estrogen concentration in pregnant women leads to the sharp increase of serum concentration of thyroid binding globulin, which affects the increase of total triiodothyronine (TT3) and total tetraiodothyronine (TT4) [21]. Thyrotropin (TSH) is decreased at the beginning of pregnancy and is increased again at the end of pregnancy, reaching the antenatal concentration, and then usually remains stable throughout pregnancy [18, 22]. One study has proposed that the large release of xanthine leads to anxiety [23]. However, there is still insufficient evidence about the changes of thyroid hormone and the occurrence of postpartum depression.

Postpartum depression changes some relevant indicators. However, there are still some problems about the relationship between inflammatory factors, thyroid hormone and xanthine on the short-term and long-term effects of postpartum depression. Clarifying the changes of key indicators of postpartum depression and drug intervention will more effectively help pregnant women out of depression, which has important clinical significance. This study explored multi-dimensional indicators for detection and comparison, such as thyroid function indicators, inflammatory factors and xanthine. Moreover, we collected clinical information of patients, including maternal age, fetal sex and feeding mode, and conducted relevant analysis, trying to find the key factors leading to postpartum depression, to provide evidence support for the clinical intervention of patients with postpartum depression.

MATERIAL AND METHODS

Patient inclusion and ethical approval

Inclusion criteria: 1. Pregnant women aged 18 and above; 2. Within 20 weeks of pregnancy; 3. The current residence is more than 1 year, and there is no long-term relocation plan in other areas within the next 1 year; 4. Birth check-up and delivery in our hospital; 5. Sign informed consent. Exclusion criteria: 1. Previous history of mental disorders; 2. Have a history of serious central nervous system diseases; 3. Suffering from serious physical diseases; 4. Have a history of psychoactive drug abuse.

Pregnant women who came to Ningxiang people's Hospital from 2020 to 2021 were selected to collect the basic information of patients and completed the self-rating depression scale (SDS) before 20 weeks of pregnancy. If the prenatal SDS score is ≥ 53, it will be excluded and will not participate in the follow-up study. Clinical registration has been carried out and the registration number is 2021001.

Study design and scoring criteria

The puerperal women who met the above criteria were evaluated by Edinburgh Depression Scale (EPDS) at 42 days after delivery, and blood samples were collected. The serums were separated after centrifugation at 3000 r/min for 4 min. The serum levels of triiodothyronine (T3), tetraiodothyronine (T4) and TSH were measured by enzyme-linked immunosorbent assay. Immunoturbidimetry on automatic biochemical analyzer was used to detect interleukin-1 β (IL-1β), interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP) and xanthine levels. All operations were carried out in strict accordance with the operating steps in the kit instructions.

For SDS, the cut-off value of SDS standard score is 53 points, of which 53–62 points are mild depression, 63––72 points are moderate depression, and more than 73 points are severe depression. All subjects are scored with EPDS self-rating scale, which includes 10 items, and each item is divided into four levels: never 0, occasionally 1, often 2, always 3, with a total score of 0–30. If the total score of EPDS is less than 9, it is normal and 10 ~12 points are the tendency of postpartum depression, and the total score ≥ 13 points can be diagnosed as postpartum depression. The higher the total score, the more serious the degree of depression.

Data statistical analysis

SPSS 21.0 software was used for statistical analysis of the data. The measurement data in line with normal distribution were expressed by mean standard deviation. Independent sample t-test was used for comparison between groups, and χ^2 was used for comparison between counting data groups. Pearson correlation analysis was used for the correlation between EPDS score and laboratory test indexes. The difference was statistically significant with $p < 0.05$.

RESULTS

The incidence rate of postnatal depression in women

A total of 139 pregnant women agreed and participated in this study. Incomplete records of basic information, incomplete SDS score, prenatal SDS ≥ 53 score and loss of blood sample records were excluded. The last 56 participants conducted this follow-up study (Fig. 1). The average age (± SD) of these 56 pregnant women was 27.3 ± 4.8 years. According to the EPDS score, the patients were divided into normal group (EPDS < 9), depression tendency group (9 ≤ EPDS < 13) and depression group (EPDS > 13). Five days after delivery, 10 of the 56 pregnant women had depression tendency, and

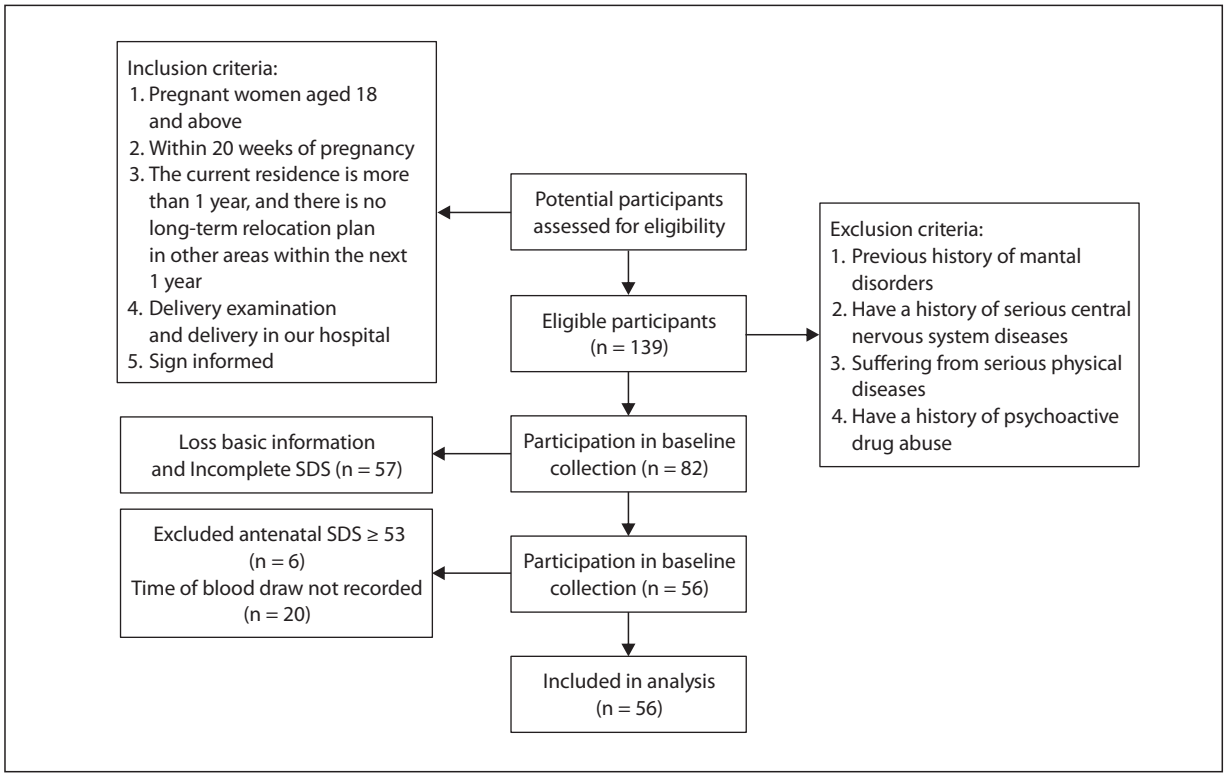


Figure 1. Consort flow diagram is illustrated; SDS — self-rating depression scale

Table 1. Basic data of pregnant women in each group

	EPDS < 9	9 ≤ EPDS < 12	EPDS ≥ 13	p value
Number (56)	34 (60.7%)	10 (17.9%)	12 (21.4%)	/
Age	27.3 ± 4.6	26.6 ± 6.2	27.7 ± 4.7	> 0.05
Feeding mode				
Breast feeding	12	3	4	/
Artificial feeding	2	4	1	/
Mix feeding	20	3	7	/
Infant gender satisfaction				
Yes	34	10	12	/
No	0	0	0	/

EPDS — Edinburgh Depression Scale

12 had depression. In our study group, the incidence rate of postnatal depression was 21.4% (Tab.1). The difference in age, feeding pattern and gender satisfaction of the three groups was not significant ($p > 0.05$) (Tab. 1).

Triiodothyronine (T3), tetraiodothyronine (T4) and thyrotropin (TSH) in the serum of pregnant women with depression

At 42 days postpartum, the thyroid function indexes T3, T4 and TSH in the serum of pregnant women with EPDS ≥ 9, including postpartum depression tendency and postpartum depression, were slightly higher than those in the normal group (EPDS < 9), but there was no significant difference between these two groups ($p > 0.05$) (Tab. 2). Further detections found that the inflammatory factors and hs-CRP in the serum of the depression groups were lower than those in the normal control group. The levels of IL-1 β, IL-6 and TNF-α were higher than that in the normal control group, but there was no significant difference between these two groups ($p > 0.05$) (Tab. 3).

Table 2. Comparison of thyroid function indexes

	EPDS < 9	EPDS ≥ 9	p value
Serum T3 [ng/dL]	1.63 ± 0.13	1.71 ± 0.18	0.2
Serum T4 [mg/dL]	0.90 ± 0.11	0.96 ± 0.16	0.32
Serum TSH [mU/L]	1.19 ± 0.56	1.39 ± 0.50	0.37

EPDS — Edinburgh Depression Scale; T3 — triiodothyronine; T4 — tetraiodothyronine; TSH — thyrotropin

Table 3. Comparison of inflammatory factor test results

	EPDS < 9	EPDS ≥ 9	p value
Serum hs-CRP [mg/mL]	18.90 ± 6.60	17.68 ± 3.90	0.61
Serum IL-1β [pg/mL]	2.36 ± 0.74	2.49 ± 0.42	0.62
Serum IL-6 [pg/mL]	15.65 ± 13.06	22.37 ± 27.14	0.43
Serum TNF-α [pg/mL]	7.66 ± 1.70	8.57 ± 1.95	0.23

EPDS — Edinburgh Depression Scale; CRP — C-reactive protein

Xanthine levels were higher in the serum of pregnant women with depression

As mentioned above, we analyzed the xanthine in the serum of pregnant women in EPDS ≥ 9 and EPDS < 9 groups. We found that the xanthine value in EPDS ≥ 9 group was higher than that in the normal group, and the p value was 0.09, which was close to 0.05. Moreover, we systematically analyzed the data of xanthine and found that the xanthine value in the depression group (9 ≤ EPDS < 13) was higher than that in the normal group (EPDS < 9), but there was no significant difference between these two groups ($p > 0.05$). The xanthine value in the depression group (EPDS ≥ 13) was also higher than that in the depression tendency group (9 ≤ EPDS < 13). Similarly, there was no significant difference between these two groups ($p > 0.05$). The xanthine value in the depression group (EPDS ≥ 13) was significantly higher than that in the normal group (EPDS < 9), and the difference between these two groups was statistically significant ($p < 0.05$) (Tab. 4 and 5).

DISCUSSION

Postpartum depression is a common and serious mental disorder, with a worldwide incidence rate of 13% ~ 19% [24]. This disease usually has a latent onset and is not easy to find. When the symptoms are mild to moderate and the behavior of seeking help is discouraged and diluted, postpartum depression can develop into severe and may even lead to suicide [25]. Postpartum depression is a serious risk to mothers and infants because it can lead to maternal mental disorders, infanticide and even suicide. Moreover, it has a significant negative impact on the mother infant relationship, the infant emotional, behavioral and cognitive development [26, 27]. Children with postpartum depression are more likely to have behavioral and emotional problems, which should be highly valued by clinical psychiatrists and obstetricians [28]. Therefore, early detection, early prevention and timely treatment are the main methods to treat postpartum depression, and exploring the etiology of postpartum depression is the key to prevention and treatment.

Edinburgh Depression Scale score is one of the most widely used postpartum depression screening scales at home and abroad, including mood, fun, self-blame, anxiety, fear, insomnia, coping ability, sadness, crying and self-injury [29]. Within 6 weeks postpartum, the total score of EPDS below 9 is normal, and the score of 9~12 is postpartum depression, which needs attention, follow-up and re-evaluation in the near future. Postpartum depression can be diagnosed if the total score is ≥ 13 [30]. There was no significant difference in age, feeding mode and satisfaction with fetal gender among the three groups ($p > 0.05$).

Postpartum depression is the result of multiple factors such as biological factors and social psychological factors [31]. The results of this study demonstrated that the thyroid function indexes T3, T4 and TSH in the EPDS ≥ 9 group were slightly higher than those in the normal group (EPDS < 9). There was no significant difference between these two groups, which was consistent with the clinical study that thyroxine could not correct postpartum depression. Changes in the immune system, especially inflammatory cytokines, play an important role in postpartum depression. IL-1β, IL-6 and hs-CRP are pro-inflammatory cytokines, which play an important role in the occurrence and development of immunity and inflammation [32, 33]. Our results showed that compared with the control group, the hs-CRP, IL-1β,

Table 4. Comparison of xanthine test results

	EPDS < 9[1]	EPDS ≥ 9[2]	
		9 ≤ EPDS < 12[3]	EPDS ≥ 13[4]
Serum xanthine (mean ± SD) [pmol/L]	393.61 ± 154.63	496.93 ± 116.57	
		442.32 ± 142.59	551.55 ± 52.76
p value	/	0.09[12]	
	0.55[13]	0.15[34]	0.04[41]*

EPDS — Edinburgh Depression Scale; SD — standard deviation; [1]represent EPDS < 9; [2]represent EPDS ≥ 9; [3]represent 9 ≤ EPDS < 12; [4]EPDS ≥ 13; [41]there is statistical significance between EPDS ≥13 groups and EPDS < 9

Table 5. Xanthine in postpartum depression test results

	Number	Age	Serum xanthine (mean ± SD)
EPDS < 9	34	27.29 ± 4.64	374.35 ± 108.65
EPDS ≥ 13	12	27.67 ± 4.74	549.53 ± 40.76
p value	/	0.9	0.03*

EPDS — Edinburgh Depression Scale; SD — standard deviation;
*represent statistical significance

IL-6 and TNF-α levels in maternal serum with EPDS ≥ 9 group were slightly higher, but there was no statistically significant difference. Therefore, the specific mechanism of serum inflammatory factors in the pathogenesis of postpartum depression still needs to expand the number of samples for further research and exploration.

Stress interferes with immune cells and affects the abnormal metabolism of immune cells, resulting in anxiety and depression [23]. Studies have shown that in animal models, stress interference leads to the rupture of T cell mitochondria and an increase of xanthine level, while xanthine acts on the amygdala and leads to mental problems [23]. The systematic analysis of xanthine data in this study found that the xanthine value of depression prone group (9 ≤ EPDS < 13) was higher than that of normal group (EPDS < 9), and the xanthine value of depression group was also higher than that of depression prone group, but there was no statistical significance between these two groups ($p > 0.05$). The xanthine value of depression group was significantly higher than that of normal group. This shows that the increase of xanthine may lead to the occurrence of postpartum depression. In the follow-up, we will further expand the number of samples to clarify the effect of xanthine on postpartum depression and provide new directions and ideas for clinical intervention of postpartum depression.

CONCLUSIONS

In conclusion, xanthine levels in patients with postpartum depression were increased significantly, and thyroid function indexes and some inflammatory indexes did not change significantly. The follow-up timely detection and intervention of maternal xanthine may help to reduce the incidence of postpartum depression and benefit the health of mothers and infants. Altogether, the xanthine level could be useful as an indicator of the risk of postpartum depression.

Article information and declarations

Data availability statement

The data are available from the corresponding author upon reasonable request.

Ethics statement

The study was approved by the Ethical Committee of Ningxiang people's Hospital.

Author contributions

L.Z. designed this study, performed the experiment and drafted the manuscript. B.Z. and P.W. searched for the literature and made the figures and tables. L.S. drafted the manuscript, designed this study and supervised this work. All authors approved the final manuscript.

Acknowledgements

Not applicable.

Conflict of interest

None.

REFERENCES

1. Drevets WC, Wittenberg GM, Bullmore ET, et al. Immune targets for therapeutic development in depression: towards precision medicine. Nat Rev Drug Discov. 2022; 21(3): 224–244, doi: 10.1038/s41573-021-00368-1, indexed in Pubmed: 35039676.
2. Bangasser DA, Cuarenta A. Sex differences in anxiety and depression: circuits and mechanisms. Nat Rev Neurosci. 2021; 22(11): 674–684, doi: 10.1038/s41583-021-00513-0, indexed in Pubmed: 34545241.
3. Wang F, Zhu H, Yang X, et al. Effects of internet-based cognitive behavioral therapy on postpartum depression: A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2022; 101(9): e28964, doi: 10.1097/MD.0000000000028964, indexed in Pubmed: 35244060.
4. Weingarten S, Diop S, Specht C, et al. Differences in interactional behaviour in postpartum depression with and without pre-existing mental disorder. Compr Psychiatry. 2021; 108: 152248, doi: 10.1016/j.comppsych.2021.152248, indexed in Pubmed: 34044326.
5. Huang X, Luo S, Wang H. Effects of the non-pharmacological interventions of traditional Chinese medicine on postpartum depression: A protocol for systematic review and network meta-analysis. Medicine (Baltimore). 2022; 101(9): e28939, doi: 10.1097/MD.0000000000028939, indexed in Pubmed: 35244051.
6. Opie RS, Uldrich AC, Ball K. Maternal postpartum diet and postpartum depression: a systematic review. Matern Child Health J. 2020; 24(8): 966–978, doi: 10.1007/s10995-020-02949-9, indexed in Pubmed: 32367245.
7. Anokye R, Acheampong E, Budu-Ainooson A, et al. Prevalence of postpartum depression and interventions utilized for its management. Ann Gen Psychiatry. 2018; 17: 18, doi: 10.1186/s12991-018-0188-0, indexed in Pubmed: 29760762.
8. Edvinsson Å, Skalkidou A, Hellgren C, et al. Different patterns of attentional bias in antenatal and postpartum depression. Brain Behav. 2017; 7(11): e00844, doi: 10.1002/brb3.844, indexed in Pubmed: 29201545.
9. Worthen RJ, Beurel E. Inflammatory and neurodegenerative pathophysiology implicated in postpartum depression. Neurobiol Dis. 2022; 165: 105646, doi: 10.1016/j.nbd.2022.105646, indexed in Pubmed: 35104645.
10. Zeng Q, Wang XH, Yang LP, et al. Shengxuening oral iron supplementation for the treatment of renal anemia: a systematic review. J Transl Int Med. 2020; 8(4): 245–254, doi: 10.2478/jtim-2020-0037, indexed in Pubmed: 33511051.
11. Semiz A, Ozgun Acar O, Cetin H, et al. Suppression of inflammatory cytokines expression with bitter melon () in tnbs-instigated ulcerative colitis. J Transl Int Med. 2020; 8(3): 177–187, doi: 10.2478/jtim-2020-0027, indexed in Pubmed: 33062594.
12. Raghupathy R, Kalinka J. Cytokine imbalance in pregnancy complications and its modulation. Front Biosci. 2008; 13: 985–994, doi: 10.2741/2737, indexed in Pubmed: 17981605.
13. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010; 67(5): 446–457, doi: 10.1016/j.biopsych.2009.09.033, indexed in Pubmed: 20015486.
14. Blackmore ER, Moynihan JA, Rubinow DR, et al. Psychiatric symptoms and proinflammatory cytokines in pregnancy. Psychosom Med. 2011; 73(8): 656–663, doi: 10.1097/PSY.0b013e31822fc277, indexed in Pubmed: 21949424.
15. Leff-Gelman P, Mancilla-Herrera I, Flores-Ramos M, et al. The immune system and the role of inflammation in perinatal depression. Neurosci Bull. 2016; 32(4): 398–420, doi: 10.1007/s12264-016-0048-3, indexed in Pubmed: 27432060.
16. Simpson W, Steiner M, Coote M, et al. Relationship between inflammatory biomarkers and depressive symptoms during late pregnancy and the early postpartum period: a longitudinal study. Braz J Psychiatry. 2016; 38(3): 190–196, doi: 10.1590/1516-4446-2015-1899, indexed in Pubmed: 27579595.
17. Shelton MM, Schminkey DL, Groer MW. Relationships among prenatal depression, plasma cortisol, and inflammatory cytokines. Biol Res Nurs. 2015; 17(3): 295–302, doi: 10.1177/1099800414543821, indexed in Pubmed: 25230746.
18. Konstantakou P, Chalarakis N, Valsamakis G, et al. Associations of thyroid hormones profile during normal pregnancy and postpartum with anxiety, depression, and obsessive/compulsive disorder scores in euthyroid women. Front Neurosci. 2021; 15: 663348, doi: 10.3389/fnins.2021.663348, indexed in Pubmed: 34421508.
19. Szpunar MJ, Parry BL. A systematic review of cortisol, thyroid-stimulating hormone, and prolactin in peripartum women with major depression. Arch Womens Ment Health. 2018; 21(2): 149–161, doi: 10.1007/s00737-017-0787-9, indexed in Pubmed: 29022126.
20. Groer MW, Vaughan JH. Positive thyroid peroxidase antibody titer is associated with dysphoric moods during pregnancy and postpartum. J Obstet Gynecol Neonatal Nurs. 2013; 42(1): E26–E32, doi: 10.1111/j.1552-6909.2012.01425.x, indexed in Pubmed: 23167615.
21. Andersen SL, Knøsgaard L, Handberg A, et al. Maternal adiposity, smoking, and thyroid function in early pregnancy. Endocr Connect. 2021; 10(9): 1125–1133, doi: 10.1530/EC-21-0376, indexed in Pubmed: 34414900.
22. Wang JW, Liao XX, Li T. Thyroid autoimmunity in adverse fertility and pregnancy outcomes: timing of assisted reproductive technology in AITD women. J Transl Int Med. 2021; 9(2): 76–83, doi: 10.2478/jtim-2021-0001, indexed in Pubmed: 34497747.
23. Fan KQ, Li YY, Wang HL, et al. Stress-Induced metabolic disorder in peripheral CD4 t cells leads to anxiety-like behavior. Cell. 2019; 179(4): 864–879.e19, doi: 10.1016/j.cell.2019.10.001, indexed in Pubmed: 31675497.
24. Norhayati MN, Hazlina NH, Asrenee AR, et al. Magnitude and risk factors for postpartum symptoms: a literature review. J Affect Disord. 2015; 175: 34–52, doi: 10.1016/j.jad.2014.12.041, indexed in Pubmed: 25590764.
25. Gastaldon C, Solmi M, Correll CU, et al. Risk factors of postpartum depression and depressive symptoms: umbrella review of current evidence from systematic reviews and meta-analyses of observational studies. Br J Psychiatry. 2022; 221(4): 591–602, doi: 10.1192/bjp.2021.222, indexed in Pubmed: 35081993.
26. Mammenga E, Hansen KA. Complementary and alternative treatments for perinatal depression. S D Med. 2021; 74(11): 506–512, indexed in Pubmed: 35008136.
27. Marconcin P, Peralta M, Gouveia ÉR, et al. Effects of exercise during pregnancy on postpartum depression: a systematic review of meta-analyses. Biology (Basel). 2021; 10(12), doi: 10.3390/biology10121331, indexed in Pubmed: 34943246.
28. Clare CA, Yeh J. Postpartum depression in special populations: a review. Obstet Gynecol Surv. 2012; 67(5): 313–323, doi: 10.1097/OGX.0b013e318259cb52, indexed in Pubmed: 22624779.
29. Zhao L, Chen J, Lan L, et al. Effectiveness of telehealth interventions for women with postpartum depression: systematic review and meta-analysis. JMIR Mhealth Uhealth. 2021; 9(10): e32544, doi: 10.2196/32544, indexed in Pubmed: 34617909.
30. Navarro P, Ascaso C, Garcia-Esteve L, et al. Postnatal psychiatric morbidity: a validation study of the GHQ-12 and the EPDS as screening tools. Gen Hosp Psychiatry. 2007; 29(1): 1–7, doi: 10.1016/j.genhosppsych.2006.10.004, indexed in Pubmed: 17189737.
31. Masmoudi J, Charfeddine F, Trabelsi S, et al. [Postpartum depression: prevalence and risk factors. A prospective Study concerning 302 Tunisian parturients]. Tunis Med. 2014; 92(10): 615–621, indexed in Pubmed: 25860676.
32. Kendall-Tackett K. A new paradigm for depression in new mothers: the central role of inflammation and how breastfeeding and anti-inflammatory treatments protect maternal mental health. Int Breastfeed J. 2007; 2: 6, doi: 10.1186/1746-4358-2-6, indexed in Pubmed: 17397549.
33. Chao J, Cui S, Liu C, et al. Detection of early cytokine storm in patients with septic shock after abdominal surgery. J Transl Int Med. 2020; 8(2): 91–98, doi: 10.2478/jtim-2020-0014, indexed in Pubmed: 32983931.

VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2024, vol. 95, no. 6, 473–478

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/gpl.97034

Congenital malformations of the female genital organs

Wiktoria Klimanek[1], Agnieszka Drosdzol-Cop[2]

[1]*Clinical Department of Gynecology, Obsterics and Subdepartment of Oncological Gynecology, Independent Public Health Care, Kedzierzyn-Kozle, Poland*

[2]*Chair and Department of Gynecology, Obsterics and Oncological Gynecology, Medical University of Silesia in Katowice, Poland*

ABSTRACT

Congenital malformations of the female genital organs are rare anomalies and their incidence is estimated to be up to 7% in the general population. Müllerian ducts abnormalities are one of the causes of infertility and occur in approximately 16% of women with recurrent miscarriages. Sex development disorders are diagnosed at different stages of the patient's life depending on the accompanying ailments. Alarming signs of genital malformations include primary amenorrhea or dysmenorrhea, dyspareunia, and periodic abdominal pain.

Keywords: congenital malformations; female genital; uterine septum; mayer-rokitansky-kűster-hauser; androgen insensitivity syndrome syndrome; ohvira syndrome

Ginekologia Polska 2024; 95, 6: 473–478

INTRODUCTION

Congenital malformations of the female genital organs are rare anomalies and their incidence is estimated to be up to 7% in the general population. Müllerian ducts abnormalities are one of the causes of infertility and occur in approximately 16% of women with recurrent miscarriages [1]. Sex development disorders are diagnosed at different stages of the patient's life depending on the accompanying ailments. Alarming signs of genital malformations include primary amenorrhea or dysmenorrhea, dyspareunia, and periodic abdominal pain.

There are two main classifications of female genital organs defects:

1. European Society of Human Reproducion and Embryology (ESHRE)/European Society for Gynaecological Endoscopy (ESGE) classification (Tab. 1–4);
2. Classification of Müllerian anomalies American Society for Reproductive Medicine (ASRM).

VAGINAL SEPTUM

There are two types of vaginal septum:

1. Transverse — the incidence of this anomaly is estimated at approximately 1:40 000 to 1:84 000 births, so it is a defect that occurs rarely [2]. It is usually located at a height of 2/3 of the upper part of the vagina. A perforated and non-perforated form can be distinguished among the transverse vaginal septum. One of the first alarming symptoms is primary amenorrhea. Importantly, the transverse septum of the vagina is often oligo- or asymptomatic until the first menstrual bleeding occurs. The outflow of menstrual blood is blocked mechanically, hence very severe, periodic abdominal pain in adolescent girls. Rarely, this defect is recognized as early as in the neonatal period. The main symptom of the disease is then dilation of the uterus and vagina by the accumulating mucous secretion referred to as hydrometrocolpos [2]. The perforated vaginal septum is characterized by less severe adverse symptoms compared to the non-perforated septum. In women with the above-mentioned type of anomaly, menstrual bleeding is prolonged due to the presence of fenestration in the septum compared to healthy women [2];
2. Longitudinal — often diagnosed accidentally during childbirth or during gynecological examination. The main symptom associated with this anomaly is dyspareunia. Often, this defect is so clinically insignificant, asymptomatic and does not bring pain to the patient that its diagnosis occurs accidentally. This anomaly coexists in 25% with the bicornuate uterus [3].

Corresponding author:
Wiktoria Klimanek
Clinical Department of Gynecology, Obsterics and Subdepartment of Oncological Gynecology, Independent Public Health Care, Kedzierzyn-Kozle, Poland
e-mail: wklimanek@gmail.com

Received: 20.08.2023 Accepted: 31.08.2023 Early publication date: 22.01.2024

Table 1. Uterine defects distinguished according to the European Society of Human Reproducion and Embryology (ESHRE)/ /European Society for Gynaecological Endoscopy (ESGE) classification

Uterine defects	
Class U0	Correct uterus
Class U1	Dysmorphic uterus: T-shape, child, of another shape
Class U2	Uterus with partial or complete septum
Class U3	Bicornuate uterus partially, completely separated or bicornuate
Class U4	Unicornuate uterus with residual horn or without a residual horn
Class U5	Plastic uterus with residual cavity or without residual cavity
Class U6	Non-classified

Table 2. Cervix defects distinguished according to the European Society of Human Reproducion and Embryology (ESHRE)/ /European Society for Gynaecological Endoscopy (ESGE) classification

Cervix defects	
Class C0	Correct cervix
Class C1	Cervix with septum
Class C2	"Correct" double cervix
Class C3	Unilateral cervix aplasia
Class C4	Cervix aplasia

Table 3. Vaginal defects distinguished according to the European Society of Human Reproducion and Embryology (ESHRE)/ /European Society for Gynaecological Endoscopy (ESGE) classification

Vaginal defects	
Class V0	Correct vagina
Class V1	Longitudinal non-closing vaginal septum
Class V2	Longitudinal closing vaginal septum
Class V3	Transverse vaginal septum; obstructed hymen
Class V4	Vaginal aplasia

Table 4. Classification of Müllerian anomalies American Society for Reproductive Medicine (ASRM)

Class I	Segmental hipoplasia/agenesia of vagina, uterus, fallopian tubes, complex
Class II	Unicornuate uterus
Class III	Double uterus
Class IV	Completely or partially bicornuate uterus
Class V	Completely or partially uterus septus
Class VI	Acruate uterus
Class VII	Defects induced by exposure to diethylstilbestrol

Complications

Lack of menstrual blood outflow results in hematoma in the cavity and cervix. If the surgical intervention is not undertaken quickly enough, then the risk of damage to the fallopian tubes increases significantly, which in the future may lead to fertility problems [4].

Treatment

Treatment of the transverse vaginal septum is based on surgical excision and end-to-end vaginal anastomosis. The procedure is planned when the patient is able to continue treatment with the use of dilators after the surgery. Dilators prevent secondary vaginal narrowing after surgery. The publications also present a method with leaving the catheter 22 after surgery and the use of cream with estrogens, which allows proper healing of the postoperative wound and reduces the risk of postoperative vaginal stenosis. Other methods of surgical removal of the septum include laparoscopic resection and abdominal-vaginal access surgery [4].

NON-PERFORATED HYMEN

This defect occurs with a frequency of about 1 in 1000 women's births [5]. The fetal malformation of the non-perforated hymen is largely manifested only during adolescence in girls. In newborns, the absence of hymen perforation is so oligosymptomatic that this anomaly is rarely diagnosed during this period of life.

Symptoms

Diagnostics of the defect consists in a carefully collected medical history and ultrasound imaging of retained menstrual blood, most often in the uterine cavity and vagina. This can also be seen in the uterine cavity.

The main symptoms reported by young patients are periodic abdominal pain and primary amenorrhea. During the gynecological examination, an organized, mobile at palpation mass and a bruised hymen are noticeable.

Compression of accumulated menstrual blood can lead to problems with urination. In extreme cases, it is possible to develop hydronephrosis and urinary retention leading to acute kidney injury. Other reported symptoms include back pain and constipation problems [5].

Treatment

Treatment involves in-patient surgical incision of the hymen, due to the risk of iatrogenic infection. The following methods of treatment of non-perforated hymen are described in the literature: hymenotomy using electrocoagulation or CO2 laser, possible with a cross or annular incision [5].

CONGENITAL UTERINE DEFECTS

Uterine defects are divided into congenital and acquired. According to studies, congenital uterine defects are the cause of from 7% to 28% of recurrent pregnancy losses [6]. There is a partial septum and a complete septum of the uterus. The screening test is a 2D ultrasound, and in the case of suspected uterine defects, a 3D ultrasound is used. Not only the cavity but also the fundus of the uterus should be assessed in detail. Sonohisterography, hysteroscopy, and laparoscopy are also useful, while magnetic resonance imaging is the gold standard in the diagnosis of genital malformations. A patient with U2 and U5 defects should be diagnosed for concomitant urinary tract defects. One of the more common concomitant defects is renal agenesis, which increases the risk of developing pregnancy-induced hypertension and preeclampsia [6].

UTERINE SEPTUM

The most common cause of approximately 6–16% among uterine malformations leading to recurrent pregnancy loss is the presence of a septum resulting from a partial or complete lack of resorption of the medial septum between the two ducts before week 20 [6]. The definition of the uterine septum according to the ESHRE classification, as muscular incision depth > 50% differs from the definition according to the ASRM classification. In order to unify the definition of the uterine septum, the Congenital Uterine Malformation by Experts (CUME) group defined the uterine septum as the presence of an incision to a depth of > 10 mm [7]. In addition, this defect should be differentiated with the arcuate uterus, the definition of which is based on the diagnosis of a uterine fundus depression of 1 to 1.5 centimeters.

The presence of a uterine septum, although asymptomatic on a daily basis, is associated with fertility problems. Patients are at increased risk of preterm birth and even pregnancy loss [8]. In this group, more frequent intrauterine limitations of fetal growth and premature separation of the placenta [7] were observed.

Treatment

The gold standard in treatment is hysteroscopic electroresection of the uterine septum. Recent controversial research among women with a history of recurrent pregnancy loss or primary infertility, defined as inability to conceive during the last 12 months, has not shown that the procedure in this group of women increased the number of live births compared to the expectant management. There were also no significant differences in the duration of pregnancy and preterm delivery in women after hysteroscopic electroresection of the uterine septum compared to women who did not undergo this procedure. Removal of the septum reduces the risk of abnormal positioning of the fetus, but does not reduce the risk of pregnancy loss or premature birth [8, 9]. However, in the light of the insufficiently large group of respondents in the above-mentioned study and other limitations, it was decided to maintain hysteroscopic septal resection as the preferred method of treatment in women with a history of obstetric failure who plan a pregnancy [7].

BICORNUATE UTERUS

Similar consequences for abnormal development of pregnancy may coexist as a result of the presence of a bicornuate uterus. The aforementioned uterine anomaly is usually asymptomatic and diagnosed only during pregnancy due to obstetric complications [3]. A pregnant woman with a bicornuate uterus should be monitored due to the proven higher risk of pregnancy loss in the first and second trimester, low birth weight of the newborn or premature birth even before the 28th week of pregnancy [3].

Treatment of bicornuate uterus

Abdominal metroplasty with the Strassman method results in a reduced risk of fetal loss. An alternative to this method is a laparoscopic modification of the Strassman method. Surgical treatment is recommended for women with a history of pregnancy loss [10]. The recommended method of termination of pregnancy is caesarean section due to the significant risk of rupture of the uterus [11]. Yes, Strassman metroplasty increases the chances of maintaining pregnancy by changing the morphology of the uterus, but the patient should be informed about possible late complications of the procedure occurring during the intra-natal period. These include, but are not limited to, an increased risk of anterior or ingrown placenta, as well as life-threatening haemorrhage due to abnormal systolic function and impaired response to vasoconstrictors [11].

UNICORNUATE UTERUS

Unicornuate uterus belongs to only 10% of all uterine defects. It is possible to have a second horn in residual form without a uterine cavity present. Another example of the anomaly is the presence of a residual horn with an active endometrium that does not communicate with the uterine cavity. The consequence of this is painful menstruation and hematoma due to lack of menstrual blood outflow as opposed to the presence of a unicornuate uterus without a residual horn, which is usually asymptomatic. Studies also indicate a higher risk of developing pelvic endometriosis in women with a unicornuate uterus with a residual horn compared to women with a uterus without a functional horn. In the given research groups, there were no differences in the incidence of adenomyosis, although it occurs much more often in patients with a unicornuate uterus compared to women with a properly shaped uterus [12].

Also in this case, the pregnancy of women with a unicornuate uterus is eligible for high-risk pregnancies, due to significantly more frequent miscarriages and a lower rate of live births. Childbirth before the 37th week of pregnancy and termination of pregnancy by caesarean section due to abnormal positioning of the fetus are also more often observed. In addition, the risk of postpartum hemorrhage is higher due to the more frequent occurrence of ingrown placenta [13].

Treatment

Treatment of the uterine anomaly described requires laparoscopic resection of the residual horn. The procedure reduces the risk of an ectopic pregnancy developing first in the residual horn, which can lead to rupture and life-threatening hemorrhage. A reduced risk of developing adenomyosis after the procedure [12] has also been proven.

DOUBLE UTERUS

The incidence of this defect ranges from 0.3% to 5% in the population. In this group of women, two cervices and an elongated vaginal septum are more common [14]. Double uterus with unilateral obstructed vagina and renal anomaly occurring on the same, usually left side, is referred to as Herlyn-Werner-Wunderlich syndrome or OHVIRA (Obstructed hemivagina and ipsilateral renal anomaly). This is a rare congenital malformation of the Müller ducts. Approximately 92% of cases have renal agenesis, while about 8% have polycystic dysplasia of the kidney [15]. Like other uterine anomalies, it manifests itself in adolescence with severe abdominal pain due to blockage of menstrual blood outflow in the uterine cavity and vagina. Before puberty, girls may report a feeling of a tumor in the vagina and a problem of urinary incontinence. Among patients with OHVIRA syndrome, we can distinguish two types of the disease due to the degree of obstructed hemivagina. Patients with complete vaginal obstruction are at increased risk of developing peritoneal hematoma and fallopian hematoma. On the other hand, in patients with incomplete obstructed hemivagina, symptoms often appear only a few years after the first menstrual period. The complaints reported at that time concern abnormal, often purulent vaginal discharge and symptoms of ascending infection [16]. There is evidence of an increased risk of cancer in patients with OHVIRA syndrome. A higher incidence of adenocarcinoma of the obstructed cervix and clear cell carcinoma of the obstructed part of the vagina has been demonstrated. Magnetic resonance imaging remains the gold standard in diagnostics, as in other defects.

MAYER-ROKITANSKY-KŰSTER-HAUSER SYNDROME

Müllerian duct agenesis occurs at a frequency of 1:5000 live births of women [17]. It is characterized by vaginal and uterine agenesis in women with normal karyotype 46 XX and female phenotype and developed secondary features.

Symptoms

In most cases, the syndrome remains asymptomatic until puberty due to primary amenorrhea despite properly developing secondary features due to retained ovarian function. The ovarian location is atypical, usually lateral due to the absence of the fallopian tubes. Sick women do not only have psychological problems due to problems with gender identification. They also struggle with dyspareunia due to impossible vaginal penetration.

Mayer-Rokitansky-Küster-Hauser syndrome can be classified as:

1. type 1 classic — isolated uterine and upper vaginal aplasia or residual vagina. The cause of cyclic abdominal pain may be aplastic uterine buds with an active endometrium, which occur in some cases. The residual uterus is subject to pathological processes that may lead to the development of fibroids and adenomyosis and endometriosis;
2. non-classical type 2 — is associated with extra-genital symptoms. The most common defects are those involving the kidneys, among which unilateral renal agenesis and the less common horseshoe kidney, single kidney and double kidney, are distinguished. Accompanying defects of the skeletal system are ribs aplasia, hemispheric vertebrae and Klippel-Feil syndrome manifested mainly by cervix shortening [17]. Defects of clinical importance are heart anomalies, which include mitral valve regurgitation, pulmonary valve stenosis, atrial septal defect, and aortopulmonary septal defect, the so-called aortopulmonary window.

Type 2 Mullerian duet aplasia, unilateral renal aplasia and cervicothoracic somite dysplasia (MURCS) syndrome includes:

- Müllerian ducts aplasia;
- malformations of the urinary system manifesting as a unilateral kidney;
- anomaly of cervico-thoracic somites.

Very rarely, VACTERL association occurs with Mayer-Rokitansky-Küster-Hauser syndrome, *i.e.* the co-occurrence of defects of the vertebrae, kidneys, heart and limbs as well as anal and esophageal atresia as well as tracheoesophageal fistula [18].

Treatment

Treatment of MRKH syndrome can be divided into invasive and non-invasive treatment. In the first place, we introduce dilator therapy to expand the vaginal recess. Frank's method is a first-line treatment due to fewer complications and relatively high efficacy. It is important to start therapy only at the moment of full awareness and emotional readiness

for intercourse by the patient. Invasive treatment involves the production of a vagina to allow for painless sexual contact. The Vecchietti technique is often performed as a first-line invasive therapy using the constant pressure of the so-called olive to produce the vagina and can be performed from a laparoscopic approach. The Davydov-Moore method uses peritoneal recesses to produce the vagina. It provides great comfort to the patient due to the proper hormonal response and adequate hydration of the neovagina. The McIndoe technique allows you to achieve the result using anthological skin grafting from the buttocks or abdominal cavity. Methods of producing neovagina from the ileum section and oral mucosa [19] are also described. Despite the use of autologous tissues and a low rate of complications, patients after surgery are recommended to continue treatment with dilators due to the possibility of secondary vaginal stenosis.

Another problem that young women suffering from MRKH syndrome have to face is infertility. In 2012, the first successful uterine transplant was carried out, enabling the offspring of patients with the described syndrome to be born [19].

ANDROGEN INSENSITIVITY SYNDROME

The syndrome is the most common cause of gender development disorders in people with the 46 XY karyotype.

The virilization period occurs between the 8th and 14th week of pregnancy. The disorder occurring in the described syndrome occurs as a result of mutation of the androgen receptor gene located on the Xq11-12 chromosome, mostly based on the mother's germline [20].

Symptoms

The syndrome can be divided into the following types:

1. CAIS total androgen insensitivity syndrome — manifested by the female phenotype. There is a development of the external female genital organs — the vagina and labia, while the internal genital organs, *i.e.* the uterus, fallopian tubes and the upper part of the vagina, are not formed. This is due to the conversion of testosterone produced by the current testes to estradiol and receptor insensitivity to androgens. Normal breast development occurs, while low levels of androgens in the blood result in underdevelopment of the nipples. Phenotypic girls are higher than healthy girls due to the gene controlling the growth of GCY present on the Y chromosome, as well as poor pubic and axillary hair and gynoid obesity [20]. The diagnosis of CAIS can be made in the prenatal period after demonstrating the 46 XY karyotype and the presence of male external genitalia or in puberty due to primary amenorrhea. Elevated levels of AMH and testosterone in the newborn's serum raise suspicions. The syndrome is often accidentally diagnosed at the time of inguinal hernia surgery in girls because gonads are present within the inguinal canal in 48% of CAIS cases. In about 35% of cases, the testes are located within the abdominal cavity, while they are rarely detected in the major labia [21];
2. Partial androgen insensitivity syndrome (PAIS) benign androgen insensitivity syndrome — characterized by residual androgen receptor function, which leads only to partial masculinization of the external genitalia. Patients are brought up as men, therefore the treatment consists in testosterone and dihydrotestosterone substitution. This means that the external genitalia can also vary from enlarged labia to smaller penis size;
3. Mild androgen insensitivity syndrome (MAIS) partial androgen insensitivity syndrome — this is the mildest and least recognized type. There is masculinization of the genitals, and the presence of micropenis and gynecomastia is the observed abnormality. However, the syndrome often remains asymptomatic, and infertility is the main problem faced by male patients [19]. It is the problem of infertility that is often the first cause of starting diagnostics for gender development disorders.

Treatment

Treatment is not only based on constant psychological care due to the increased risk of depressive disorders and gender identification problems. Due to the increased risk of carcinogenesis after puberty, it is necessary to perform a gonadectomy after puberty process. This has a positive effect on the process of creating phenotypically female characteristics, as well as bone mineralization, osteogenesis and proper functioning of the cardiovascular system [22]. Girls use the aforementioned dilators to widen the vagina due to the short, blindly terminated vagina. Hormone replacement therapy is used in patients after gonadectomy and in children who underwent the procedure before the end of puberty. Currently, in people suffering from CAIS, it is recommended to use estradiol in transdermal form and continue until menopause in healthy women [21]. In order to increase the symptoms of virilization of external organs in patients with PAIS, treatment with high doses of testosterone or dihydrotestosterone is used in the intramuscular or local supply. The maximum effect of therapy is usually achieved after about six months, after which hormone therapy is used in maintenance doses [20]. Hyperlipidemia should be monitored during hormone therapy.

People suffering from gender development disorders are at an increased risk of developing germ cell tumors. It has been proven that the development of neoplastic lesions depends, among others, on age — the risk of carcinogenesis increases significantly after puberty, which is why laparoscopic gonadectomy is recommended for phenotypic women.

If the testicles are left, the risk increases to 50%. Ultrasound is the method of choice for monitoring gonads, while MRI scan [20] is recommended for assessing abdominal gonads.

Defects of external and internal genitalia in girls require in-depth diagnostics. In everyday practice, it is important to perform 2D and 3D ultrasound in the doctor's office, but it should be remembered that the gold standard for the diagnosis of congenital defects of the female genital organs is magnetic resonance imaging due to the possibility existence of concomitant defects. Auxiliary methods include diagnostic laparoscopy, hysterosalpingography or hysteroscopy. Appropriate diagnosis and treatment tailored to the patient's problem not only eliminates pain, but also significantly increases the comfort of life.

Article information and declarations

Author contributions

W.K.: study design, interpretation of results, manuscript preparation; A.D.C.: study conception, analysis of results.

Funding

Private.

Acknowledgments

None.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Passos Id, Britto RL. Diagnosis and treatment of müllerian malformations. Taiwan J Obstet Gynecol. 2020; 59(2): 183–188, doi: 10.1016/j.tjog.2020.01.003, indexed in Pubmed: 32127135.
2. Yadav G, Agrawal N, Binit S, et al. Transverse vaginal septum presenting as secondary amenorrhoea: a rare clinical presentation. BMJ Case Rep. 2020; 13(8), doi: 10.1136/bcr-2020-235374, indexed in Pubmed: 32843410.
3. Kaur P, Panneerselvam D. Bicornuate Uterus. StatPearls May 15, 2023.
4. Barut A, Hirsi ZA, Yusuf K. Management of an isolated complete imperforate transverse vaginal septum: A case report. Int J Surg Case Rep. 2022; 100: 107744, doi: 10.1016/j.ijscr.2022.107744, indexed in Pubmed: 36265424.
5. Abdelrahman H, Feloney M. Imperforate Hymen. StatPearlsuly July 11, 2022.
6. Carbonnel M, Pirtea P, Ziegler Dde, et al. Uterine factors in recurrent pregnancy losses. Fertility and Sterility. 2021; 115(3): 538–545, doi: 10.1016/j.fertnstert.2020.12.003.
7. Noventa M, Spagnol G, Marchetti M, et al. Uterine Septum with or without Hysteroscopic Metroplasty: Impact on Fertility and Obstetrical Outcomes—A Systematic Review and Meta-Analysis of Observational Research. Journal of Clinical Medicine. 2022; 11(12): 3290, doi: 10.3390/jcm11123290.
8. Rikken J, Kowalik CR, Emanuel MH, et al. Septum resection versus expectant management in women with a septate uterus: an international multicentre open-label randomized controlled trial. Human Reproduction. 2021; 36(5): 1260–1267, doi: 10.1093/humrep/deab037.
9. Rikken JFW, Verhorstert KWJ, Emanuel MH, et al. Septum resection in women with a septate uterus: a cohort study. Hum Reprod. 2020; 35(7): 1578–1588, doi: 10.1093/humrep/dez284, indexed in Pubmed: 32353142.
10. Gulavi E, Kyende Mutiso S, Mariara Muriuki C, et al. Successful Pregnancy Outcome after Open Strassman Metroplasty for Bicornuate Uterus. Case Rep Obstet Gynecol. 2018; 2018: 4579736, doi: 10.1155/2018/4579736, indexed in Pubmed: 30018833.
11. Zhang C, Wang X, Jiang H, et al. Placenta percreta after Strassman metroplasty of complete bicornuate uterus: a case report. BMC Pregnancy Childbirth. 2021; 21(1): 95, doi: 10.1186/s12884-021-03540-y, indexed in Pubmed: 33514327.
12. Tellum T, Bracco B, De Braud LV, et al. Reproductive outcome in 326 women with unicornuate uterus. Ultrasound Obstet Gynecol. 2023; 61(1): 99–108, doi: 10.1002/uog.26073, indexed in Pubmed: 36099518.
13. Ma YC, Law KS. Pregnancy in a Non-Communicating Rudimentary Horn of Unicornuate Uterus. Diagnostics (Basel). 2022; 12(3), doi: 10.3390/diagnostics12030759, indexed in Pubmed: 35328312.
14. Crowley CM, Botros K, Hegazy IF, et al. Uterine didelphys: diagnosis, management and pregnancy outcome. BMJ Case Rep. 2021; 14(3), doi: 10.1136/bcr-2021-242233, indexed in Pubmed: 33782076.
15. Samanta A, Rahman SM, Vasudevan A, et al. A novel combination of OHVIRA syndrome and likely causal variant in UMOD gene. CEN Case Rep. 2023; 12(2): 249–253, doi: 10.1007/s13730-022-00754-7, indexed in Pubmed: 36417174.
16. Herlin M, Petersen M, Brännström M. Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome: a comprehensive update. Orphanet Journal of Rare Diseases. 2020; 15(1), doi: 10.1186/s13023-020-01491-9.
17. Bjørsum-Meyer T, Herlin M, Qvist N, et al. Vertebral defect, anal atresia, cardiac defect, tracheoesophageal fistula/esophageal atresia, renal defect, and limb defect association with Mayer-Rokitansky-Küster-Hauser syndrome in co-occurrence: two case reports and a review of the literature. J Med Case Rep. 2016; 10(1): 374, doi: 10.1186/s13256-016-1127-9, indexed in Pubmed: 28003020.
18. Bjørsum-Meyer T, Herlin M, Qvist N, et al. Vertebral defect, anal atresia, cardiac defect, tracheoesophageal fistula/esophageal atresia, renal defect, and limb defect association with Mayer-Rokitansky-Küster-Hauser syndrome in co-occurrence: two case reports and a review of the literature. J Med Case Rep. 2016; 10(1): 374, doi: 10.1186/s13256-016-1127-9, indexed in Pubmed: 28003020.
19. Avino A, Răducu L, Tulin A, et al. Vaginal Reconstruction in Patients with Mayer-Rokitansky-Küster-Hauser Syndrome-One Centre Experience. Medicina (Kaunas). 2020; 56(7), doi: 10.3390/medicina56070327, indexed in Pubmed: 32630225.
20. Batista RL, Costa EM, Rodrigues Ad, et al. Androgen insensitivity syndrome: a review. Arch Endocrinol Metab. 2018; 62(2): 227–235, doi: 10.20945/2359-3997000000031, indexed in Pubmed: 29768628.
21. Xiao X, Zhou Y. Complete androgen insensitivity Syndrome: A rare case report. Asian Journal of Surgery. 2023: S1015-9584(23)00651-6.
22. Barros B, Oliveira L, Surur C, et al. Complete androgen insensitivity syndrome and risk of gonadal malignancy: systematic review. Annals of Pediatric Endocrinology & Metabolism. 2021; 26(1): 19–23, doi: 10.6065/apem.2040170.085.

VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2024, vol. 95, no. 6, 479–482

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/gpl.97556

Breastfeeding and fatty liver — is there any association?

Weronika Powroslo[1], Magdalena Wymyslo-Filipecka[2], Agnieszka Drosdzol-Cop[1], Brygida Adamek[2]

[1]Department and Clinical Department of Gynecology, Obstetrics and Oncological Gynecology, Faculty of Health Sciences in Katowice, Medical University of Silesia in Katowice, Poland

[2]Department of Basic Medical Sciences, Faculty of Public Health in Bytom, Medical University of Silesia in Katowice, Bytom, Poland

ABSTRACT

The campaign to promote the natural feeding of infants, at least for the first six months of life, conducted over recent years has deep justification from a medical point of view. Numerous gynecological and pediatric societies around the world recommend breastfeeding as the most appropriate way of feeding infants. It has been proven that the benefits of this type of nutrition go beyond nutritional aspects, proper growth and development. The list of long-term metabolic benefits, which include reducing the incidence of obesity, allergies, infections and diabetes, is constantly growing. It has been shown that the method of feeding infants using various mechanisms may influence the tendency of the liver to accumulate fatty compounds and develop fatty liver disease with its metabolic consequences leading to liver failure, cirrhosis and hepatocellular carcinoma. This is an important discovery due to the growing obesity epidemic in adults and children. Metabolic dysfunction — associated fatty liver disease (MAFLD) has become the most common cause of chronic liver disease, affecting 25% of the global population. The results of studies conducted in recent years have shown the protective effect of breastfeeding on the risk of developing MAFLD later in life in both children and breastfeeding women. New scientific reports provide the basis for qualifying breastfeeding as a modifiable risk factor for MAFLD.

Keywords: breastfeeding; metabolic diseases; fatty liver

Ginekologia Polska 2024; 95, 6: 479–482

INTRODUCTION

The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) recommend breastfeeding as the most appropriate way to feed newborns and infants.

It should be the sole method of nutrition for the first six months of life, beginning within the first hour after birth [1]. The same recommendations are also presented by the American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP) and the Committee on Nutrition of the European Society of Gastroenterology, Hepatology and Nutrition of Children the European Society for Pediatric Gastroenterology Hepatology and Nutrition, (ESPGHAN) [2, 3]. The benefits of breastfeeding go beyond nutritional aspects. In addition to conditioning the proper growth and development of the young body, it brings several health benefits. It has been proven that naturally fed children are less likely to suffer from obesity, allergies, infections and diabetes [4]. According to data published by WHO, overweight and obesity occur in 5.7% to 40% of children, depending on the population studied. It has been estimated that obesity may be a problem for up to approximately 40 million children under five years of age, with prevalence in younger children [5].

Obesity-related diseases are a risk factor for the development of metabolic dysfunction associated with fatty liver disease — MAFLD [6]. It is characterized by excessive accumulation of fat in the liver, associated with insulin resistance and obesity, defined as the histological presence of hepatic

Corresponding author:
Magdalena Wymyslo-Filipecka
Department of Basic Medical Sciences, Faculty of Public Health in Bytom, Medical University of Silesia in Katowice, Piekarska 18 St. 41–902 Bytom, Poland
e-mail: magdalena.wymyslo@gmail.com

Received: 23.09.2023 Accepted: 3.11.2023 Early publication date: 1.03.2024

steatosis > 5% of hepatocytes in the absence of alcohol abuse. Initially, the disease was called nonalcoholic fatty liver diseases (NAFLD) — and this term is used in many earlier scientific papers — but recently the nomenclature was changed to MAFLD. Metabolic dysfunction associated with fatty liver disease is a serious public health problem because it is a risk factor for many metabolic diseases, including cardiovascular diseases, which are still the leading cause of death in the world [6], type 2 diabetes, and, except of all, is the most frequently diagnosed liver disease in humans [7].The excessive accumulation of lipids in the liver leads to impaired functioning of this organ and, consequently, to fibrosis and the development of hepatocellular carcinoma [8, 9].

A characteristic feature of MAFLD is fatty liver as a result of disturbances in lipid homeostasis in the liver. Excessive amounts of free fatty acids accumulated as a result of increased lipolysis of adipose tissue and de novo lipogenesis exceed the ability of the liver to oxidize them or secrete in the form of very low-density lipoproteins. This set of metabolic disorders is a consequence of the coincidence of various environmental, genetic and epigenetic factors [6]. MAFLD has become the most common chronic liver disease, affecting 25% of adults in the world [2]. According to the results of general population studies, it is diagnosed in 7.6–9.6% of children. However, studies conducted in pediatric obesity clinics indicate a higher frequency of up to 34.2% [6].

BREASTFEEDING — METABOLIC EFFECT IN CHILDREN

The fetal period and the first few months after birth are the "plastic" age. It is often referred to as a "window of opportunity". This initial period of life is particularly important because the intensively developing organism is highly susceptible to environmental pressure and must adapt to changing stimuli [10]. The research conducted so far allows us to conclude that prenatal, perinatal and postnatal events may have a significant impact on an individual's human metabolic health, both in the medium- and long-term perspectives.

Breastfeeding remains the most appropriate alimentation pattern for infants. Breast milk has a unique composition best suited to the baby's needs. It contains numerous bioactive compounds, including oligosaccharides, which protect against the development of many disorders occurring in childhood, including obesity, type 2 diabetes and other metabolic diseases [5]. The composition of breast milk is not constant. It changes dynamically depending on various variables, such as gestation, the postpartum period and the suckling period. Although the main function of milk is to provide nutrients for the infant's intensive development, mother's milk has also been described as the first probiotic food. It contains over 200 phylotypes of probiotic bacteria [4]. Additionally, human oligosaccharides promote the growth of beneficial bacteria *Bifidobacteria* and *Bacteroides* [5]. Feeding a newborn this way not only enriches the microbiota but also has a real impact on the composition and activity of the intestinal flora. This may be crucial in preventing the development of metabolic syndrome later in life [4]. Scientific research has shown that the composition of the "adult-type" microbiota depends on many factors including perinatal conditions, which include the method of delivery, type of breastfeeding and the use of antibiotics. Additionally, it has been shown that the mother's diet, age, metabolic status, family genetics and lifestyle have a strong influence on the infant's intestinal flora [10].

Intestinal dysbiosis, *i.e.* permanent modification of the microbiome, has been recognized, based on the results of research in experimental adult murine models and adult patients, as an important factor in the development of many systemic diseases, for example obesity and MAFLD. Unfortunately, it has been poorly documented in the pediatric population so far [6]. It has been proven that intestinal flora affects the use of nutrients supplied with food, the immune system, and the expression of host genes. Therefore, it is reasonable to assume that microbiota may influence the development of MAFLD at a young age.

Although there is not enough data supporting the relationship between neonatal feeding and the development of MAFLD later in life, the type of infant feeding, and the duration of breastfeeding may have a profound impact on the risk of developing MAFLD. The protective effect of breast-feeding on the development of NAFLD was observed in 2009 by Nobili et al. [11], which examined the relationship between infant feeding pattern (breastfeeding vs formula feeding and duration of breastfeeding) and the development of fatty liver in children aged from 3 to 18 years. Of the 191 study participants with confirmed NAFLD, 91 were naturally breastfed and the duration of breastfeeding was usually around 8 months. It was noted that the probability of developing non-alcoholic steatohepatitis (NASH), a more severe form of NAFLD, and liver fibrosis was lower in breastfed children and decreased with the length of breastfeeding. The benefit of breastfeeding was also demonstrated in the Western Australian Pregnancy (Raine) Cohort Study, where just over 15% of 1170 adolescents aged 17 years were diagnosed with fatty liver by ultrasound. It was estimated that breastfeeding for at least 6 months without starting formula before 6 months of age was independently associated with a 40% lower risk of developing NAFLD in adolescence. On the other hand, early introduction of formula feeding, before 6 months of age, was associated with a 70% higher risk of NAFLD [7]. The results of the Ragama Health Study, a cohort study of 499 14-year-olds living in an urban area

of Sri Lanka, indicated a short period of breastfeeding (less than 4 months) as a factor significantly associated with a higher risk of NAFLD [12]. The association of artificial infant feeding with the severity of adverse liver changes in children aged 5–12 years with biopsy-proven NAFLD was reported in a cross-sectional study of 182 patients at the Bambino Gesu Children's Hospital in Rome. The results of an extensive analysis considering many factors, including pregnancy, genetic, familial, nutritional and lifestyle factors have identified the lack of breastfeeding among the significant factors predisposing to the development of NASH and liver fibrosis [13]. Ayonrinde et al. [7], analyzing a group of 1170 adolescents aged 17 years in the Western Australian Pregnancy (Raine) Cohort Study, concluded that to reduce the risk of NAFLD being diagnosed during adolescence, it is recommended to breastfeed for at least 6 months, avoid early feeding with complementary milk and achieving the mother's normal BMI before pregnancy. These data suggest that infants who breastfed for less than six months were much more likely to develop NAFLD later in life. The latest systematic review on the relationship between breastfeeding and the development of NAFLD in later life has led to the conclusion that breastfeeding may be a protective factor for the development of NAFLD if it lasts long enough, *i.e.* at least 6 months [14]. On the other hand, Abeysekera et al. [10] in their parental negative control study did not replicate previous work that found a strong association between neither any nor exclusive over six months breastfeeding nor NAFLD.

Except of breastfeeding, extensive studies were focused on assessing the relationship between the mother's nutritional status and the occurrence of metabolic diseases, such as obesity, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) in her offspring [10].

BREASTFEEDING — METABOLIC EFFECTS IN MOTHERS

The relationship between infant feeding and the risk of developing chronic diseases in mothers has been the subject of numerous studies for many years. During recent studies, the protective effect of breastfeeding on the development of NAFLD in the mother has also been documented. In a study by Ajmera et al. [15] with the participation of 844 women, it was shown that a longer duration of lactation, especially longer than 6 months, is associated with a significantly lower probability of NAFLD in middle age. Similar conclusions were drawn from the results of a nationwide study by Goh et al. carried out on a cohort of nearly 7,000 Korean women. It was noted that women who breastfed for more than one month were less likely to develop NAFLD. Moreover, a gradual decrease in the risk of NAFLD was shown with the extension of the lactation period [16]. The benefits of breastfeeding for the mother have not been as extensively documented as in the case of infants. Future research should determine the effect of lactation on the development of NAFLD and other liver diseases.

SUMMARY

Metabolic dysfunction associated with fatty liver disease is an increasing cause of cirrhosis and hepatocellular carcinoma and the most common liver disease in children, which can represent an aggressive phenotype of the disease and lead to the requirement for liver transplantation. The constantly growing incidence of MAFLD in Western countries and Asia in the absence of effective therapy prompts the search for modifiable risk factors. The evidence of a protective effect of breastfeeding on MAFLD for both mothers and their offspring, cited in this article, extends the list of potential long-term benefits of breastfeeding and may be an argument to include breastfeeding as a weapon in the fight against the growing MAFLD epidemic.

Article information and declarations

Author contributions

BA — 25%: concept, article draft; MWF — 25%: concept, analysis, corresponding author; ADC — 25%: concept, article draft; WP — concept, analysis, article draft.

Funding

None.

Acknowledgements

None.

Conflict of interest

The authors declare that they have no competing interests.

Supplementary material

None.

REFERENCES

1. WHO. Breastfeeding [Internet]. https://www.who.int/health-topics/breastfeeding#tab=tab_1 (23.09.2023).
2. Młodawska M, Młodawski J, Pazera G, et al. Breast is the best — what gynecologist should know about breastfeeding. Ginekol Perinatol Prakt. 2019; 4(1): 23–33.
3. Szajewska H, Horvath A, Rybak A, et al. Breastfeeding. A position paper by the polish society for paediatric gastroenterology, hepatology and nutrition. Stand Med Pediatr. 2016; 13: 9–24.
4. Truchet S, Honvo-Houéto E. Physiology of milk secretion. Best Pract Res Clin Endocrinol Metab. 2017; 31(4): 367–384, doi: 10.1016/j.beem.2017.10.008, indexed in Pubmed: 29221566.
5. Meliț LE, Mărginean CO, Săsăran MO. The yin-yang concept of pediatric obesity and gut microbiota. Biomedicines. 2022; 10(3), doi: 10.3390/biomedicines10030645, indexed in Pubmed: 35327446.
6. Le Garf S, Nègre V, Anty R, et al. Metabolic fatty liver disease in children: a growing public health problem. Biomedicines. 2021;

9(12): 1915, doi: 10.3390/biomedicines9121915, indexed in Pubmed: 34944730.
7. Ayonrinde OT, Oddy WH, Adams LA, et al. Infant nutrition and maternal obesity influence the risk of non-alcoholic fatty liver disease in adolescents. J Hepatol. 2017; 67(3): 568–576, doi: 10.1016/j.jhep.2017.03.029, indexed in Pubmed: 28619255.
8. Rajewski P, Rajewski P, Wiciński M, et al. Non-alcoholic fatty liver disease (NAFLD): etiology, diagnosis, treatment in the light of current knowledge. Forum Med Rodzin. 2020; 14(1): 1–10.
9. Riazi K, Azhari H, Charette JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022; 7(9): 851–861, doi: 10.1016/S2468-1253(22)00165-0, indexed in Pubmed: 35798021.
10. Abeysekera KWm, Orr JG, Madley-Dowd P, et al. Association of maternal pre-pregnancy BMI and breastfeeding with NAFLD in young adults: a parental negative control study. Lancet Reg Health Eur. 2021; 10: 100206, doi: 10.1016/j.lanepe.2021.100206, indexed in Pubmed: 34806068.
11. Nobili V, Bedogni G, Alisi A, et al. A protective effect of breastfeeding on the progression of non-alcoholic fatty liver disease. Arch Dis Child. 2009; 94(10): 801–805, doi: 10.1136/adc.2009.159566, indexed in Pubmed: 19556219.
12. Rajindrajith S, Pathmeswaran A, Jayasinghe C, et al. Non-alcoholic fatty liver disease and its associations among adolescents in an urban, Sri Lankan community. BMC Gastroenterol. 2017; 17(1): 135, doi: 10.1186/s12876-017-0677-7, indexed in Pubmed: 29187144.
13. Mosca A, De Cosmi V, Parazzini F, et al. The role of genetic predisposition, programing during fetal life, family conditions, and post-natal diet in the development of pediatric fatty liver disease. J Pediatr. 2019; 211: 72–77.e4, doi: 10.1016/j.jpeds.2019.04.018, indexed in Pubmed: 31128886.
14. Querter I, Pauwels NS, De Bruyne R, et al. Maternal and perinatal risk factors for pediatric nonalcoholic fatty liver disease: a systematic review. Clin Gastroenterol Hepatol. 2022; 20(4): 740–755, doi: 10.1016/j.cgh.2021.04.014, indexed in Pubmed: 33862225.
15. Ajmera VH, Terrault NA, VanWagner LB, et al. Longer lactation duration is associated with decreased prevalence of non-alcoholic fatty liver disease in women. J Hepatol. 2019; 70(1): 126–132, doi: 10.1016/j.jhep.2018.09.013, indexed in Pubmed: 30392752.
16. Park Y, Sinn DH, Oh JH, et al. The association between breastfeeding and nonalcoholic fatty liver disease in parous women: a nation-wide cohort study. Hepatology. 2021; 74(6): 2988–2997, doi: 10.1002/hep.32034, indexed in Pubmed: 34192367.

VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2024, vol. 95, no. 6, 483–501

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/gpl.97888

Translation and cross-cultural adaptation of the Get Active Questionnaire for Pregnancy (kwestionariusz "Badź Aktywna w Ciąży") to support physical activity among pregnant women in Poland

Anna Szumilewicz[1], Margie H. H. Davenport[2], Anna Scholz[3], Anita Sikora-Szubert[4], Rita Santos-Rocha[5, 6], Agata Karowicz-Bilinska[4], Agnieszka Zembron-Lacny[7], Kazimierz Ciechanowski[8], Jaroslaw Krzywanski[9], Sebastian Kwiatkowski[10], Tomasz Kostka[11], Piotr Sieroszewski[12], Ewa Kwiatkowska[13]

[1]Faculty of Physical Culture, Gdansk University of Physical Activity and Sport, Poland
[2]Program for Pregnancy and Postpartum Health, Faculty of Kinesiology, Sport, and Recreation, University of Alberta, Edmonton, Canada
[3]Clinic of Obstetrics and Gynecology. Center of Postgraduate Medical Education, Warsaw, Poland
[4]Clinical Department of Pathology of Pregnancy and Department of Gynecology and Obstetrics, Medical University of Lodz, Poland
[5]Sport Sciences School of Rio Maior, Polytechnic Institute of Santarém, Rio Maior, Portugal
[6]SPRINT Sport Physical Activity and Health Research & Innovation Center, Portugal
[7]Departments of Applied Physiology and Clinical Physiology, Collegium Medicum, University of Zielona Gora, Poland
[8]Clinical Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University, Szczecin, Poland
[9]National Center for Sports Medicine, Warsaw, Poland
[10]Clinical Department of Gynecology and Obstetrics, Pomeranian Medical University, Szczecin, Poland
[11]Clinical Department of Geriatric Medicine, Medical University of Lodz, Poland
[12]Department of Gynecology and Obstetrics, Medical University of Lodz, Poland
[13]Clinical Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University, Szczecin, Poland

ABSTRACT

Physical activity during pregnancy is established to derive clinically meaningful improvements in pregnancy, childbirth, and postpartum health outcomes. Evidence-based pre-screening tools have been developed to support the implementation of physical activity programmes, and enhance communication between health care providers, exercise professionals and pregnant women. The Get Active Questionnaire for Pregnancy (GAQ-P) and the Health Care Provider Consultation Form for Prenatal Physical Activity (HCPCF) empower pregnant women to identify whether they require additional counselling from their obstetric health care provider in terms of physical activity. However, these tools are not available in Polish. This work details the process taken to translate the GAQ-P and HCPCF into Polish. Material and Methods: We followed the translation process outlined by the Translation and Cultural Adaptation International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines between August 2022 and August 2023. We formed an expert group that included representatives of the Polish Society of Sports Medicine, The Polish Society of Gynaecologists and Obstetricians, practitioners, and scientists in physical activity during pregnancy. We implemented 9 of the 10 steps recommended by ISOPR in the translation process. At the Cognitive Debriefing stage, we collected opinions on the Polish version of GAQ-P and HCPCF from 70 stakeholders on the clarity and cultural appropriateness of the translation. Results and Conclusions: Target users have positively evaluated the Polish version of GAQ-P and HCPCF. Thanks to the ISPOR methodology, we obtained a trustworthy, evidence-based screening tools, which can reduce the barriers for most women to be physically active during pregnancy.

Keywords: pregnancy; physical activity; exercise; screening tool; recommendations

Ginekologia Polska 2024; 95, 6: 483–501

Corresponding author:
Anna Szumilewicz
Faculty of Physical Culture, Gdansk University of Physical Activity and Sport, Poland
e-mail: anna.szumilewicz@awf.gda.pl

Received: 11.12.2023 Accepted: 19.12.2023 Early publication date: 24.01.2024

INTRODUCTION

Extensive research has demonstrated that regular physical activity in pregnancy (PAP) leads to positive health outcomes for the mother and child [1–3]. Key benefits listed by the World Health Organization (WHO) include decreased risk of pre-eclampsia, gestational hypertension, gestational diabetes, excessive gestational weight gain, delivery complications, and postpartum depression, and fewer neonatal complications [4]. In support of these benefits, the WHO experts recommend pregnant and postpartum women to perform at least 150 minutes of moderate-intensity aerobic physical activity a week and limit their sedentary time. They further recommend that women who, before pregnancy, habitually engaged in sports of vigorous intensity or who were physically active can continue these activities during pregnancy and postpartum as long as the pregnancy progresses without complications. Similar guidelines were published in other countries in the last few years [5]. In 2023, the Polish Association of Gynaecologists and Obstetricians and the Polish Association of Sports Medicine created joint guidelines on following current guideance outlined above, as well as incorporating more contemporary research and practical knowledge [6].

Although the vast majority of Polish women (over 90%) are aware of the beneficial effects of PAP on the course of pregnancy [7], almost half of them are inactive while pregnant [8]. Paradoxically, one of the most common causes of their inactivity is the fear for the health and safety of the foetus [9]. Based on recent meta-analyses, these fears are entirely unfounded. Prenatal exercise is not associated with miscarriage, stillbirth, neonatal death, preterm birth, preterm/prelabour rupture of membranes or low birth weight [10, 11]. However, it is important to screen for contraindications or medical reasons why prenatal physical activity may not be beneficial or must be adjusted.

Unfortunately, women do not always base their decision to start PAP on current knowledge and reliable sources of information. In Poland, at least half of women look for information about PAP on the Internet [8]. According to the Polish standard of perinatal care, obstetricians and midwives should educate women on a healthy lifestyle, including physical activity during pregnancy and after childbirth [12]. In 2012, only 1% of Polish doctors encouraged women to PAP [9]. In 2018, the statistics were better, but less than one-third of doctors instructed their pregnant patients to engage in physical activity [7]. Therefore, it seems necessary to implement tools supporting obstetric care providers in performing these professional tasks.

The Get Active Questionnaire for Pregnancy (GAQ-P) and an associated Health Care Provider Consultation Form for Prenatal Physical Activity (HCPCF) were developed in 2021 by an expert group led by Davenport et al. [13], under the affiliation of the Canadian Society of Exercise Physiology (CSEP). These evidence-based tools were designed to reduce the barriers to physical activity for most women who should and are willing to be physically active during pregnancy. The GAQ-P is a self-completed part to identify pregnant women who should seek additional counselling from their obstetric care provider about postential contraindications to PAP. The target users for these screening tools are pregnant women, obstetric care providers, policymakers, and qualified exercise professionals who guide PAP. The objective of this work was to translate the GAQ-P and and the HCPCF into Polish, and perform a cultural adaptation of theses tools.

METHODS

Based on the experiences of other authors [14], to translate the GAQ-P and the HCPCF into Polish (later referred to as the target language), we followed the translation process according to the Translation and Cultural Adaptation International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines [15]. We used the 9 of 10 suggested steps in the translation process: Preparation; Forward Translation; Reconciliation; Back Translation; Back Translation Review; Cognitive Debriefing; Review of Cognitive Debriefing Results and Finalization; Proofreading; Final Report. We skipped the so-called Harmonisation, for reasons outlined below.

The entire work, including the analysis of the opinions of various stakeholders on the Polish version of the questionnaires, was carried out following the principles of data collection and processing, including those regulated by the Personal Data Protection Act. People invited to the Cognitive Debriefing stage signed an informed consent to participate in this process before its commencement. The works lasted from August 2022 to August 2023.

Preparation

In August 2022, the first author of this paper (later referred to as the project manager) discussed the translation process with the first author of the GAQ-P and HCPCF (later referred to as the instrument developer) and obtained written permission from the CSEP to carry out this process. The GAQ-P and HCPCF in the original language were presented in the scientific session on "Physical activity in pregnancy" during the 34th International Scientific Congress of the Polish Society of Sports Medicine "From Health to Performance" in Szczecin, Poland, on the 16th of September, 2022. During the Congress, the main assumptions of this instrument were discussed, and the need to implement it on the Polish market was confirmed. To carry out this task, a group of experts was appointed. Its members included, among others, representatives of the Polish Society of Sports Medicine, The Polish Society of Gynaecologists and Obstetricians, Gdansk University of Physical Education and Sport, practitioners, and scientists in physical activity during pregnancy.

Forward translation

In October 2022, two experts conducted two independent forward translations of the original English instrument into Polish (V1 and V2, respectively; Tab. 1 and 2). Both translators were Polish native speakers and residents of Poland. Two independent translations are recommended to avoid the linguistic styles of a single person and to facilitate the detection of potential errors and divergent interpretation of ambiguous terms [15]. One of the forward translators was a researcher in exercise science and a Pregnancy and Postpartum Exercise Specialist. The second translator was a researcher in the field of medical science and a practising physician. This allowed a different translation perspective and ensured the use of professional terms specific to medical and physical activity language.

Table 1. Summary of results of translation and adaptation of the Get Active Questionnaire for Pregnancy into Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the pregnant woman

Original version	Polish version 1 (V1)	Polish version 2 (v2)
GET ACTIVE QUESTIONNAIRE FOR PREGNANCY	Kwestionariusz „Bądź aktywna w ciąży"	Kwestionariusz „Bądź aktywna w ciąży"
NAME (+ NAME OF PARENT/GUARDIAN IF APPLICABLE) [PLEASE PRINT]:	Imię i nazwisko (+ imię i nazwisko rodzica/ /opiekuna prawnego, jeśli dotyczy) [PROSZĘ WYPEŁNIĆ DRUKOWANYMI LITERAMI]:	Imię i nazwisko (Imię rodziców lub opiekunów prawnych) Drukowanymi literami
TODAY'S DATE (DD/MM/YYYY):	Dzisiejsza data (DD/MM/RRRR):	Dzisiejsza data (DD/MM/RRRR)
YOUR DUE DATE (DD/MM/YYYY):	Termin porodu (DD/MM/RRRR):	Termin porodu (DD/MM/RRRR):
NO. OF WEEKS PREGNANT:	Tydzień ciąży:	Numer zakończonych tygodni ciąży
AGE:	Wiek	Wiek
Physical activity during pregnancy has many health benefits and is generally not risky for you and your baby. But for some conditions, physical activity is not recommended. This questionnaire is to help decide whether you should speak to your Obstetric Health Care Provider (*e.g.*, your physician or midwife) before you begin or continue to be physically active	Aktywność fizyczna w czasie ciąży ma wiele korzyści zdrowotnych i najczęściej nie wiąże się z ryzykiem ani dla Pani, ani dla Pani dziecka. Jednak w niektórych sytuacjach aktywność fizyczna nie jest zalecana. Ten kwestionariusz ma pomóc Pani w podjęciu decyzji, czy przed rozpoczęciem lub kontynuacją aktywności fizycznej powinna Pani porozmawiać z lekarzem lub położną prowadzącymi ciążę	Aktywność fizyczna w czasie ciąży ma wiele zalet zdrowotnych i nie jest ryzykowna dla Ciebie i Twojego dziecka. W niektórych sytuacjach aktywność fizyczna nie jest zalecana. Ten kwestionariusz ma pomóc w podjęciu decyzji, czy przed rozpoczęciem lub kontynuacją aktywności fizycznej powinnaś porozmawiać z lekarzem prowadzącym lub położną
Please answer YES or NO to each question to the best of your ability. If your health changes as your pregnancy progresses you should fill in this questionnaire again	Proszę odpowiedzieć TAK lub NIE na każde pytanie, na tyle na ile Pani potrafi. Jeśli Pani stan zdrowia zmienia się wraz z przebiegiem ciąży, powinna Pani ponownie wypełnić ten kwestionariusz	Proszę odpowiedzieć TAK lub NIE na każde pytanie najlepiej jak potrafisz. Jeśli Twój stan zdrowia zmienia się wraz z postępem ciąży, powinnaś ponownie wypełnić ten kwestionariusz
In this pregnancy, do you have:	W tej ciąży doświadczyła Pani:	Czy w aktualnej ciąży masz schorzenia lub stany wymienione poniżej:
Mild, moderate or severe respiratory or cardiovascular diseases (*e.g.*, chronic bronchitis)?	Łagodne, umiarkowane lub ciężkie choroby układu oddechowego lub sercowo-naczyniowego (np. przewlekłe zapalenie oskrzeli)?	Łagodne, umiarkowane lub ciężkie choroby układu oddechowego lub sercowo-naczyniowego (np. przewlekłe zapalenie oskrzeli)?
Epilepsy that is not stable?	Padaczka, która nie jest ustabilizowana?	Padaczka, która nie jest stabilna?
Type 1 diabetes that is not stable or your blood sugar is outside of target ranges?	Cukrzyca typu 1, która nie jest wyrównana lub poziom cukru we krwi jest poza wartościami docelowymi?	Cukrzyca typu 1, która nie jest stabilna lub poziom cukru we krwi jest poza zalecanym zakresem?
Thyroid disease that is not stable or your thyroid function is outside of target ranges?	Choroba tarczycy, która nie jest ustabilizowana lub czynność tarczycy jest poza wartościami referencyjnymi?	Choroba tarczycy, która nie jest stabilna lub hormony tarczycy określające czynność tarczycy są poza zakresem docelowym?
An eating disorder(s) or malnutrition?	Zaburzenia odżywiania lub niedożywienie?	Zaburzenia odżywiania lub niedożywienie?
Twins (28 weeks pregnant or later)? Or are you expecting triplets or higher multiple births?	Bliźnięta (28 tydzień ciąży lub później)? Lub ciąża trojacza albo wyższa ciąża mnoga?	Bliźnięta (28 tydzień ciąży lub później)? A może spodziewasz się trojaczków lub wyższych ciąż mnogich?
Low red blood cell number (anemia) with high levels of fatigue and/or light-headedness?	Niski poziom krwinek czerwonych (niedokrwistość) przy współwystepowaniu dużego zmęczenia i/lub zawrotów głowy?	Niską liczbę czerwonych krwinek (niedokrwistość) z objawami zmęczenia i/lub zawrotów głowy?
High blood pressure (preeclampsia, gestational hypertension, or chronic hypertension that is not stable)?	Wysokie ciśnienie krwi (stan przedrzucawkowy, nadciśnienie ciążowe lub przewlekłe nadciśnienie, które nie jest ustabilizowane)?	Wysokie ciśnienie tętnicze krwi (stan przedrzucawkowy, nadciśnienie ciążowe lub przewlekłe nadciśnienie, które nie jest stabilne)?

→

Table 1. cont. Summary of results of translation and adaptation of the Get Active Questionnaire for Pregnancy into Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the pregnant woman

Original version	Polish version 1 (V1)	Polish version 2 (v2)
A baby that is growing slowly (intrauterine growth restriction)?	Dziecko, które rośnie zbyt wolno (wewnątrzmaciczne ograniczenie wzrostu płodu)?	Dziecko, które rośnie zbyt wolno (wewnątrzmaciczne ograniczenie wzrastania płodu)?
Unexplained bleeding, ruptured membranes or labour before 37 weeks?	Krwawienie z pochwy o nieznanej przyczynie, pęknięcie błon płodowych lub poród przed 37 tygodniem?	Niewyjaśnione krwawienie z dróg rodnych, pęknięcie błon płodowych lub poród przed 37 tygodniem?
A placenta that is partially or completely covering the cervix (placenta previa)?	Łożysko, które częściowo lub całkowicie zakrywa szyjkę macicy (łożysko przodujące)?	Łożysko, które częściowo lub całkowicie zakrywa szyjkę macicy (łożysko przodujące)?
Weak cervical tissue (incompetent cervix)?	Słaba tkanka szyjki macicy (niewydolna szyjka macicy)?	Słaba szyjka macicy (niewydolna szyjka macicy)?
A stitch or tape to reinforce your cervix (cerclage)?	Szew lub taśma wzmacniająca szyjkę macicy?	Szew lub taśma wzmacniająca szyjkę macicy?
In previous pregnancies, have you had:	Czy w poprzednich ciążach doświadczyła Pani:	Czy w poprzednich ciążach miałaś:
Recurrent miscarriages (loss of your baby before 20 weeks gestation two or more times)?	Nawracające poronienia (utrata dziecka przed 20 tygodniem ciąży dwa lub więcej razy z rzędu)?	Nawracające poronienia (utrata dziecka przed 20 tygodniem ciąży dwa lub więcej razy)?
Early delivery (before 37 weeks gestation)?	Przedwczesny poród (przed 37 tygodniem ciąży)?	Poród przedwczesny (przed 37 tygodniem ciąży)?
Do you have any other medical condition that may affect your ability to be physically active during pregnancy? What is the condition? Specify:	Czy ma Pani inne schorzenia, które mogą wpływać na Pani zdolność do aktywności fizycznej podczas ciąży? Proszę sprecyzować co to za problem zdrowotny:	Czy masz inne schorzenia, które mogą wpływać na twoją zdolność do aktywności fizycznej podczas ciąży? Jakie to schorzenia? Podaj:
Is there any other reason you are concerned about physical activity during pregnancy?	Czy jest jakiś inny powód, dla którego obawia się Pani aktywności fizycznej w czasie ciąży?	Czy jest jakiś inny powód, dla którego obawiasz się aktywności fizycznej w czasie ciąży?
Describe your physical activity level	Proszę opisać Pani poziom aktywności fizycznej	Opisz swój poziom aktywności fizycznej
During a typical week, what types of physical activities do you take part in (*e.g.*, swimming, walking, resistance training, yoga)?	W czasie typowego tygodnia, w jakich rodzajach aktywności fizycznej Pani uczestniczy (np. pływanie, spacery, trening oporowy/ćwiczenia kształtujące poszczególne części ciała, joga)?	W typowym tygodniu, w jakich rodzajach aktywności fizycznej uczestniczysz (np. pływanie, spacery, trening wzmacniający mięśnie, joga)?
During the same week, please describe ON AVERAGE how often and for how long you engage in physical activity of a light, moderate or vigorous intensity. See definitions for intensity below the box	W odniesieniu do tego samego tygodnia proszę opisać PRZECIĘTNIE, jak często i jak długo uprawia Pani aktywność fizyczną o niskiej, umiarkowanej lub wysokiej intensywności. Proszę zobaczyć definicje intensywności w ramce poniżej	W tym samym tygodniu proszę opisać ŚREDNIO, jak często i jak długo uprawia Pan/Pani aktywność fizyczną o lekkim, umiarkowanym lub intensywnym natężeniu. Zobacz definicje intensywności poniżej ramki
ON AVERAGE	Przeciętnie	ŚREDNIO
How physically active were you in the six months before pregnancy?	Na ile była Pani aktywna fizycznie w ciągu sześciu miesięcy przed ciążą?	Jak bardzo byłaś aktywna fizycznie w ciągu sześciu miesięcy przed ciążą?
How physically active have you been during this pregnancy?	Na ile była Pani aktywna fizycznie do tej pory w tej ciąży?	Jak bardzo byłaś aktywna fizycznie podczas tej ciąży?
What are your physical activity goals for the rest of your pregnancy?	Jakie są Pani cele związane z aktywnością fizyczną do końca ciąży?	Jaką aktywność fizyczną planujesz do końca aktualnej ciąży?
FREQUENCY (times per week)	CZĘSTOŚĆ (ile razy w tygodniu)	CZĘSTOTLIWOŚĆ (razy w tygodniu)
INTENSITY (see below for definitions)	INTENSYWNOŚĆ (proszę przeczytać definicje poniżej)	INTENSYWNOŚĆ (patrz definicje poniżej)
DURATION (minutes per session)	Czas trwania (ile minut na sesję)	Czas trwania (minuty na sesję)
Light intensity physical activity: You are moving, but you do not sweat or breathe hard, such as walking to get the mail or light gardening	Aktywność fizyczna o niskiej intensywności: Porusza się Pani, ale nie poci ani nie oddycha ciężko, na przykład chodzenie do sklepu lub lekkie prace w ogrodzie	Aktywność fizyczna o małej intensywności: Poruszasz się, ale nie pocisz się ani nie oddychasz ciężko, na przykład chodzenie po pocztę lub lekkie prace w ogrodzie
Moderate intensity physical activity: Your heart rate goes up and you may sweat or breathe hard. You can talk, but could not sing. Examples include brisk walking	Aktywność fizyczna o umiarkowanej intensywności: Pani tętno wzrasta i może się Pani pocić lub ciężko oddychać. Możesz Pani mówić, ale nie może śpiewać, np. szybki marsz	Aktywność fizyczna o umiarkowanej intensywności: Twoje tętno wzrasta i możesz się pocić lub ciężko oddychać. Możesz mówić, ale nie możesz śpiewać. Np. szybki marsz

→

Table 1. cont. Summary of results of translation and adaptation of the Get Active Questionnaire for Pregnancy into Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the pregnant woman

Original version	Polish version 1 (V1)	Polish version 2 (v2)
Vigorous intensity physical activity: Your heart rate goes up substantially, you feel hot and sweaty, and you cannot say more than a few words without pausing to breathe. Examples include fast stationary cycling and running	Aktywność fizyczna o wysokiej intensywności: Pani tętno znacznie wzrasta, czuje się Pani zgrzana i spocona, nie może Pani powiedzieć więcej niż kilka słów bez robienia przerw na oddech, np. szybką jazda na rowerze stacjonarnym lub bieganie	Aktywność fizyczna o dużej intensywności: Twoje tętno znacznie wzrasta, czujesz się gorąco i spocony i nie możesz powiedzieć więcej niż kilka słów bez robienia przerw na oddech. Np. szybka jazda na rowerze stacjonarnym i bieganie
General Advice for Being Physically Active During Pregnancy	Ogólne zalecenia dotyczące aktywności fizycznej w czasie ciąży	Ogólne porady dotyczące aktywności fizycznej w czasie ciąży
Follow the advice in the 2019 Canadian Guidelines for Physical Activity throughout Pregnancy: csepguidelines.ca/pregnancy	Należy postępować zgodnie z zalecaniami zawartymi w polskich i kanadyjskich wytycznych dotyczących aktywności fizycznej w czasie ciąży z 2019 r.	Postępuj zgodnie z radami zawartymi w polskich wytycznych dotyczących aktywności fizycznej w czasie ciąży z 2023 r.: PTGiP
It recommends that pregnant women get at least 150 minutes of moderate-intensity physical activity (resistance training, brisk walking, swimming, gardening), spread over three or more days of the week. If you are planning to take part in vigorous-intensity physical activity, or be physically active at elevations above 2500 m (8200 feet), then consult with your health care provider	Kobietom w ciąży zaleca się co najmniej 150 minut aktywności fizycznej o umiarkowanej intensywności (np. trening oporowy/ćwiczenia kształtujące poszczególne części ciała, szybki marsz, pływanie, prace w ogrodzie) rozłożonej na trzy lub więcej dni w tygodniu. Jeśli planuje Pani wziąć udział w intensywnej aktywności fizycznej lub być aktywną fizycznie na wysokości powyżej 2500 m n.p.m., należy skonsultować się z lekarzem lub położną prowadzącymi ciążę	Zaleca kobietom w ciąży co najmniej 150 minut aktywności fizycznej o umiarkowanej intensywności (trening wzmacniający mięśnie, szybki marsz, pływanie, prace w ogrodzie) rozłożonej na trzy lub więcej dni w tygodniu. Jeśli planujesz wziąć udział w intensywnej aktywności fizycznej lub być aktywnym fizycznie na wysokości powyżej 2500 m (8200 stóp), skonsultuj się ze swoim lekarzem
If you have any questions about physical activity during pregnancy, consult a Qualified Exercise Professional or your health care provider beforehand. This can help ensure that your physical activity is safe and suitable for you	Jeśli ma Pani jakiekolwiek pytania dotyczące aktywności fizycznej podczas ciąży, należy skonsultować z wykwalifikowanym instruktorem lub trenerem ćwiczeń w ciąży lub lekarzem czy położną prowadzącymi ciążę. Może to pomóc upewnić się, że Pani aktywność fizyczna jest bezpieczna i odpowiednia dla Pani	Jeśli masz jakiekolwiek pytania dotyczące aktywności fizycznej podczas ciąży, skonsultuj się wcześniej z lekarzem lub położną. Może to pomóc upewnić się, że Twoja aktywność fizyczna jest bezpieczna i odpowiednia dla Ciebie
Declaration	Oświadczenie	Deklaracja
To the best of my knowledge, all of the information I have supplied on this questionnaire is correct. If my health changes, I will complete this questionnaire again	Zgodnie z moją najlepszą wiedzą, wszystkie informacje podane przeze mnie w tym kwestionariuszu są prawidłowe. Jeśli mój stan zdrowia ulegnie zmianie, wypełnię ten kwestionariusz ponownie	Zgodnie z moją najlepszą wiedzą, wszystkie informacje podane przeze mnie w tym kwestionariuszu są prawidłowe. Jeśli mój stan zdrowia ulegnie zmianie, wypełnię ten kwestionariusz ponownie
I answered NO to all questions on Page 1. Sign and date the declaration below. Physical activity is recommended	Odpowiedziałam NIE na wszystkie pytania na stronie 1. Należy podpisać i datować poniższe oświadczenie. Aktywność fizyczna jest zalecana	Odpowiedziałem NIE na wszystkie pytania na stronie 1. Podpisz i opatrz datą poniższe oświadczenie. Zalecana jest aktywność fizyczna
I answered YES to one or more questions on Page 1 and I will speak with my health care provider before beginning or continuing physical activity. The Health Care Provider Consultation Form for Prenatal Physical Activity can be used to start the conversation (www.csep.ca/getactivequestionnaire-pregnancy)	Odpowiedziałam TAK na jedno lub więcej pytań na stronie 1 i porozmawiam z moim lekarzem lub położną przed rozpoczęciem lub kontynuacją aktywności fizycznej. Aby rozpocząć rozmowę z lekarzem lub położną, można skorzystać z„Formularza konsultacji z lekarzem lub położną w zakresie aktywności fizycznej w ciąży" (link)	Odpowiedziałem TAK na jedno lub więcej pytań na stronie 1 i porozmawiam z moim lekarzem przed rozpoczęciem lub kontynuacją aktywności fizycznej. Aby rozpocząć rozmowę, można skorzystać z Formularza konsultacji z pracownikiem opieki medycznej dotyczącej prenatalnej aktywności fizycznej (link)
I have spoken with my health care provider who has recommended that I take part in physical activity during my pregnancy. Sign and date the declaration below	Rozmawiałam z moim lekarzem lub położną, którzy zalecili mi aktywność fizyczną podczas ciąży. Należy podpisać i datować poniższe oświadczenie	Rozmawiałam z moim lekarzem, który zalecił mi aktywność fizyczną podczas ciąży. Podpisz i opatrz datą poniższe oświadczenie
NAME (+ NAME OF PARENT/GUARDIAN IF APPLICABLE) [PLEASE PRINT]:	Imię i nazwisko (Imię i nazwisko rodzica/opiekuna prawnego jeśli dotyczy (PROSZĘ WYPEŁNIĆ DRUKOWANYMI LITERAMI)	IMIĘ I NAZWISKO (+ IMIĘ I NAZWISKO RODZICA/OPIEKUNA, JEŚLI DOTYCZY) [PROSZĘ WYDRUKOWAĆ]:
SIGNATURE (OR SIGNATURE OF PARENT/GUARDIAN IF APPLICABLE):	Podpis (lub podpis rodzica lub opiekuna prawnego, jeśli dotyczy):	PODPIS (LUB PODPIS RODZICA/OPIEKUNA, JEŚLI DOTYCZY):
TODAY'S DATE (DD/MM/YYYY):	Dzisiejsza data (DD/MM/RRRR):	DZISIEJSZA DATA (DD/MM/RRRR):
TELEPHONE (OPTIONAL)	Numer telefonu (opcjonalnie)	TELEFON (OPCJONALNIE)
EMAIL (OPTIONAL):	Email (opcjonalnie)	EMAIL OPCJONALNY):

V — version

Table 2. Summary of results of translation and adaptation of The Health Care Provider Consultation Form for Prenatal Physical Activity into Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the health care provider

Original version	Polish version 1 (V1)	Polish version 2 (v2)
HEALTH CARE PROVIDER CONSULTATION FORM FOR PRENATAL PHYSICAL ACTIVITY	FORMULARZ KONSULTACJI Z LEKARZEM LUB POŁOŻNĄ W ZAKRESIE AKTYWNOŚCI FIZYCZNEJ W CIĄŻY	FORMULARZ KONSULTACYJNY ŚWIADCZENIODAWCY USŁUG ZDROWOTNYCH DOT. PRENATALNEJ AKTYWNOŚCI FIZYCZNEJ
Your patient wishes to begin or continue to be physically active during pregnancy. Your patient answered „Yes" to one or more questions on the Get Active Questionnaire for Pregnancy and has been asked to seek your advice (www.csep.ca/getactivequestionnaire-pregnancy)	Twoja pacjentka chce rozpocząć lub kontynuować aktywność fizyczną w czasie ciąży. Twoja pacjentka odpowiedziała „Tak" na jedno lub więcej pytań w Kwestionariuszu „Bądź aktywna w ciąży" i została poproszona o zasięgnięcie Twojej porady (www.csep.ca/getactivequestionnaire-pregnancy)	Pana/Pani pacjentka pragnie podjąć lub kontynuować aktywność fizyczną w czasie ciąży. Pacjentka udzieliła odpowiedzi „Tak" na co najmniej jedno pytanie w Ankiecie Podejmij Aktywność w Ciąży, w związku z czym zalecono jej zasięgnięcie porady u Pana/Pani (www.csep.ca/getactivequestionnaire-pregnancy)
Physical activity is safe for most pregnant individuals and has many health benefits. However, a small number of patients may need a thorough evaluation before taking part in physical activity during pregnancy	Aktywność fizyczna jest bezpieczna dla większości ciężarnych i przynosi wiele korzyści zdrowotnych. Jednak niewielka liczba pacjentek może wymagać dokładnej oceny przed podjęciem aktywności fizycznej w czasie ciąży	Aktywność fizyczna jest bezpieczna dla większości ciężarnych i niesie ze sobą wiele korzyści zdrowotnych. Niemniej niewielka liczba pacjentek może wymagać dokładnej oceny przed podjęciem aktywności fizycznej w trakcie ciąży
The Society of Obstetricians and Gynaecologists of Canada/Canadian Society for Exercise Physiology 2019 Canadian Guideline for Physical Activity throughout Pregnancy recommends that pregnant women get at least 150 minutes of moderate intensity physical activity each week (see next page or csepguidelines.ca/pregnancy). But there are contraindications to this goal for some conditions (see right)	Zgodnie z (The Society of Obstetricians and Gynecologists of Canada/Canadian Society for Exercise Physiology 2019) kanadyjskimi wytycznymi dotyczącymi aktywności fizycznej w okresie ciąży, kobiety w ciąży powinny wykonywać co najmniej 150 minut aktywności fizycznej o umiarkowanej intensywności każdego tygodnia (patrz następna strona lub csepguidelines.ca/pregnancy). Ale w niektórych przypadkach występują przeciwwskazania do aktywności (patrz po prawej)	Kanadyjskie Wytyczne Dotyczące Aktywności Fizycznej w Ciąży z 2019 r. Kanadyjskiego Towarzystwa Położników i Ginekologów/Kanadyjskiego Towarzystwa Wysiłku Fizycznego (SOGC/CSEP) zaleca ciężarnym podejmowanie co najmniej 150 minut aktywności fizycznej o umiarkowanej intensywności tygodniowo (patrz następna strona lub csepguidelines.ca/pregnancy). W przypadku niektórych stanów chorobowych istnieją jednakże przeciwwskazania do dążenia do tak postawionego celu
Specific concern from your patient and/or from a Qualified Exercise Professional:	Szczególne obawy pacjentki i/lub wykwalifikowanego instruktora lub trenera ćwiczeń w ciąży:	Szczególne obawy pacjentki i/lub wykwalifikowanego specjalisty ds. ćwiczeń fizycznych:
To ensure that your patient proceeds in the safest way possible, they were advised to consult with you about becoming or continuing to be physically active during pregnancy. Please discuss potential concerns you may have about physical activity with your patient and indicate in the box below any modifications you might recommend:	Aby upewnić się, że Twoja pacjentka jest aktywna w możliwie najbezpieczniejszy sposób, zalecono jej skonsultowanie się z Tobą w sprawie podjęcia lub kontynuowania aktywności fizycznej w czasie ciąży. Przedyskutuj z pacjentką potencjalne obawy, jakie możesz mieć w związku z aktywnością fizyczną, i wskaż w polu poniżej wszelkie zalecane modyfikacje:	Aby zapewnić możliwie najbezpieczniejszy przebieg ćwiczeń, pacjentce zalecono konsultację z Panem/Panią w sprawie aktywności fizycznej podczas ciąży. Prosimy o omówienie z pacjentką Pana/Pani ewentualnych obaw dotyczących aktywności fizycznej i wskazanie w polu poniżej wszelkich zalecanych modyfikacji:
Unrestricted physical activity based on the SOGC/CSEP 2019 Canadian Guidelines for Physical Activity throughout Pregnancy	Aktywność fizyczna bez modyfikacji i ograniczeń, zgodnie z kanadyjskimi wytycznymi SOGC/CSEP 2019 dotyczące aktywności fizycznej w okresie ciąży	Nieograniczona aktywność fizyczna oparta na Kanadyjskich Wytycznych Dotyczących Aktywności Fizycznej w Ciąży z 2019 r.
Progressive physical activity	Stopniowo zwiększana aktywność fizyczna	Aktywność fizyczna ze stopniowo zwiększanym obciążeniem
Recommend avoiding:	Zalecam unikanie:	Zalecam unikać:
Recommend including:	Zalecam włączenie:	Zalecam włączyć:
Recommend supervision by a Qualified Exercise Professional, if possible	W miarę możliwości zalecam nadzór ze strony wykwalifikowanego instruktora lub trenera ćwiczeń w ciąży	W miarę możliwości zalecam nadzór ze strony wykwalifikowanego instruktora rekreacji ruchowej
Refer to a physiotherapist for pain, impairment and/or a pelvic floor assessment	Zwróć się do fizjoterapeuty w celu diagnostyki w kierunku występowania bólu, dysfunkcji i/lub oceny dna miednicy	Kieruję do fizjoterapeuty w celu dokonania oceny dolegliwości bólowych, zaburzeń i/lub dna miednicy
Other comments:	Inne komentarze	Inne uwagi:
Absolute contraindications	Przeciwwskazania bezwzględne	Przeciwwskazania bezwzględne

→

Table 2. cont. Summary of results of translation and adaptation of The Health Care Provider Consultation Form for Prenatal Physical Activity into Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the health care provider

Original version	Polish version 1 (V1)	Polish version 2 (v2)
Pregnant women with these conditions should continue activities of daily living, but not take part in moderate or vigorous physical activity:	Kobiety w ciąży z poniżej wskazanymi nieprawidłowościami w przebiegu ciąży lub stanie zdrowia, powinny kontynuować codzienne czynności, ale nie powinny brać udziału w umiarkowanej lub intensywnej aktywności fizycznej:	Kobiety ciężarne obciążone tymi dolegliwościami powinny kontynuować aktywność związaną z codziennym życiem, ale nie powinny brać udziału w umiarkowanej ani energicznej aktywności fizycznej:
Ruptured membranes	Pęknięcie błon płodowych	Pęknięcie błon płodowych
Premature labour	Poród przedwczesny	Poród przedwczesny
Unexplained persistent vaginal bleeding	Niewyjaśnione uporczywe krwawienie z pochwy	Niewyjaśnione uporczywe krwawienie z pochwy
Placenta previa after 28 weeks gestation	Łożysko przodujące po 28 tygodniu ciąży	Łożysko przodujące po 28 tyg. ciąży
Preeclampsia	Stan przedrzucawkowy	Stan przedrzucawkowy
Incompetent cervix	Niewydolnośc szyjki macicy	Niewydolność cieśniowo-szyjkowa
Intrauterine growth restriction	Wewnątrzmaciczne ograniczenie wzrostu płodu	Ograniczenie wzrastania płodu
High-order multiple pregnancy (*e.g.* triplets)	Ciąża mnoga (np. trojacza)	Ciąża wielopłodowa liczniejsza niż bliźniacza (np. trojaczki)
Uncontrolled type I diabetes	Niewyrównana cukrzyca typu I	Niewyrównana cukrzyca typu 1
Uncontrolled hypertension	Niewyrównane nadciśnienie	Niewyrównane nadciśnienie
Uncontrolled thyroid disease	Niewyrównane choroby tarczycy	Niewyrównana choroba tarczycy
Other serious cardiovascular, respiratory or systemic disorder	Inne poważne zaburzenia sercowo-naczyniowe, oddechowe lub ogólnoustrojowe	Inne poważne zaburzenia sercowo-naczyniowe, oddechowe lub układowe
Relative contraindications	Względne przeciwwskazania	Przeciwwskazania względne
Pregnant women with these conditions should discuss advantages and disadvantages of physical activity with you. They should continue physical activity, but modify exercises to reduce intensity and/or duration	Kobiety w ciąży z tymi schorzeniami powinny omówić z Tobą korzyści i zagrożenia związane z aktywnością fizyczną. Powinny kontynuować aktywność fizyczną, jednakże, jeśli zasadne, modyfikując ćwiczenia, aby zmniejszyć ich intensywność i/lub czas trwania	Kobiety ciężarne obciążone tymi dolegliwościami powinny omówić z Panem/Panią zalety i wady aktywności fizycznej. Powinny kontynuować aktywność fizyczną, ale zmodyfikować wykonywane ćwiczenia tak, by zmniejszyć ich intensywność i/lub czas trwania
Recurrent pregnancy loss	Nawracające poronienia	Powtarzająca się utrata ciąży
Gestational hypertension	Nadciśnienie ciążowe	Nadciśnienie ciążowe
A history of spontaneous preterm birth	Spontaniczny poród przedwczesny w wywiadzie	W wywiadzie spontaniczny poród przedwczesny
Mild/moderate cardiovascular or respiratory disease	Łagodna/umiarkowana choroba układu krążenia lub układu oddechowego	Łagodna/umiarkowana choroba układu krążenia lub oddechowego
Symptomatic anemia	Niedokrwistość objawowa	Objawowa niedokrwistość
Malnutrition	Niedożywienie	Niedożywienie
Eating disorder	Zaburzenia odżywiania	Zaburzenia odżywiania
Twin pregnancy after the 28th week	Ciąża bliźniacza po 28 tygodniu	Ciąża bliźniacza po 28 tygodniu
Other significant medical conditions	Inne znaczące schorzenia	Inne istotne stany chorobowe
SOGC/CSEP 2019 CANADIAN GUIDELINE FOR PHYSICAL ACTIVITY THROUGHOUT PREGNANCY	SOGC/CSEP 2019 KANADYJSKIE WYTYCZNE DOTYCZĄCE AKTYWNOŚCI FIZYCZNEJ W CIĄŻY	SOGC/CSEP 2019 KANADYJSKIE WYTYCZNE DOTYCZĄCE AKTYWNOŚCI FIZYCZNEJ W CIĄŻY
The evidence-based guideline outlines the right amount of physical activity women should get throughout pregnancy to promote maternal, fetal, and neonatal health	Oparte na dowodach wytyczne określają odpowiednią ilość aktywności fizycznej, którą kobiety powinny wykonywać przez całą ciążę, aby promować zdrowie matki, płodu i noworodka	Te oparte na dowodach wytyczne określają właściwą objętość aktywności fizycznej ciężarnych w celu promowania zdrowia matki, płodu i noworodka
Research shows the health benefits and safety of being active throughout pregnancy for both mother and baby. Physical activity is now seen as a critical part of a healthy pregnancy. Following the guideline can reduce the risk of pregnancy-related illnesses such as depression, by at least 25%, and of developing gestational diabetes, high blood pressure and preeclampsia by 40%	Badania pokazują korzyści zdrowotne i bezpieczeństwo bycia aktywną przez cały okres ciąży zarówno dla matki, jak i dziecka. Aktywność fizyczna jest obecnie postrzegana jako kluczowy element zdrowej ciąży. Stosowanie się do wytycznych może zmniejszyć ryzyko wystąpienia chorób związanych z ciążą, takich jak depresja, o co najmniej 25%, oraz rozwoju cukrzycy ciążowej, nadciśnienia tętniczego i stanu przedrzucawkowego o 40%	Badania wskazują na korzyści zdrowotne oraz na bezpieczeństwo zachowania aktywności w trakcie ciąży zarówno dla matki, jak i dziecka. Obecnie dostrzega się kluczowe znaczenie aktywności fizycznej dla zachowania zdrowej ciąży. Przestrzeganie wytycznych może zmniejszyć ryzyko wystąpienia chorób związanych z ciążą, na przykład depresji o co najmniej 25%, a cukrzycy ciążowej, wysokiego ciśnienia krwi i stanu przedrzucawkowego o 40%

→

Table 2. cont. Summary of results of translation and adaptation of The Health Care Provider Consultation Form for Prenatal Physical Activity into Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the health care provider

Original version	Polish version 1 (V1)	Polish version 2 (v2)
Pregnant women should get at least 150 minutes of moderate-intensity physical activity each week over at least three days per week. But even if they do not meet that goal, they are encouraged to be active in a variety of ways every day. Please visit csepguidelines.ca/pregnancy for more information. The guideline makes six recommendations:	Kobiety w ciąży powinny tygodniowo wykonywać co najmniej 150 minut aktywności fizycznej o umiarkowanej intensywności przez co najmniej trzy dni w tygodniu. Ale nawet jeśli nie osiągną tego celu, należy je zachęcać do jakiejkolwiek aktywności każdego dnia. Więcej informacji można znaleźć na stronie csepguidelines.ca/pregnancy. Wytyczne zawierają sześć zaleceń:	Kobiety w ciąży powinny podejmować tygodniowo co najmniej 150 minut aktywności fizycznej o umiarkowanej intensywności przez co najmniej trzy dni danym w tygodniu. Jednak nawet jeśli nie osiągają tego celu, to i tak zaleca się im utrzymanie wielorakiej aktywności każdego dnia. Więcej informacji można znaleźć na stronie csepguidelines.ca/pregnancy. Wytyczne obejmują sześć zaleceń:
All women without contraindication should be physically active throughout pregnancy. Specific subgroups were examined: • women who were previously inactive • women diagnosed with gestational diabetes mellitus • women categorized as overweight or obese (pre-pregnancy body mass index ≥ 25 kg/m^2)	Wszystkie kobiety bez przeciwwskazań powinny być aktywne fizycznie przez cały okres ciąży. Zbadano poszczególne podgrupy: • kobiety, które wcześniej były nieaktywne • kobiety ze zdiagnozowaną cukrzycą ciążową • kobiety z nadwagą lub otyłością (wskaźnik masy ciała sprzed ciąży ≥ 25 kg/m^2)	Wszystkie kobiety, które nie mają przeciwwskazań, powinny być aktywne fizycznie przez cały okres ciąży. Zbadano konkretne podgrupy: • kobiety, które wcześniej nie utrzymywały aktywności • kobiety z rozpoznaną cukrzycą ciążową • kobiety z nadwagą lub otyłością (wskaźnik masy ciała przed ciążą ≥ 25 kg/m^2)
Pregnant women should accumulate at least 150 minutes of moderate-intensity physical activity each week to achieve clinically meaningful health benefits and reductions in pregnancy complications	Kobiety w ciąży powinny tygodniowo poświęcać co najmniej 150 minut na aktywność fizyczną o umiarkowanej intensywności, aby osiągnąć klinicznie znaczące korzyści zdrowotne i zmniejszyć liczbę powikłań ciąży	Pacjentki w ciąży powinny uprawiać aktywność fizyczną o umiarkowanej intensywności przez co najmniej 150 minut tygodniowo, by osiągnąć klinicznie istotne korzyści zdrowotne i zmniejszyć częstość występowania powikłań ciążowych
Physical activity should be accumulated over a minimum of three days per week; however, being active every day is encouraged	Aktywność fizyczna powinna być wykonywana przez co najmniej trzy dni w tygodniu; jednakże zaleca się jej podejmowanie każdego dnia	Aktywność fizyczną należy stosować przez co najmniej trzy dni w tygodniu, jednakże zachęca się do jej podejmowania każdego dnia
Pregnant women should incorporate a variety of aerobic and resistance training activities to achieve greater benefits. Adding yoga and/or gentle stretching may also be beneficial	Kobiety w ciąży powinny wykonywać różnorodne ćwiczenia aerobowe i oporowe/ wzmacniające poszczególne grupy mięśniowe, aby osiągnąć większe korzyści. Korzystne może być również dodanie jogi i/lub delikatnego rozciągania	Kobiety w ciąży powinny wykonywać różnorodne ćwiczenia aerobowe i siłowe, by osiągnąć większe korzyści. Korzystne może być również stosowanie jogi i/lub delikatnego rozciągania
Pelvic floor muscle training (*e.g.*, Kegel exercises) may be performed on a daily basis to reduce the risk of urinary incontinence. Instruction in proper technique is recommended to obtain optimal benefits	Trening mięśni dna miednicy (np. ćwiczenia Kegla) można wykonywać codziennie, aby zmniejszyć ryzyko nietrzymania moczu. W celu uzyskania optymalnych korzyści zaleca się instruktaż odpowiedniej techniki	Trening mięśni dna miednicy (np. ćwiczenia Kegla) wykonywać można codziennie w celu zmniejszenia ryzyka nietrzymania moczu. Optymalne efekty uzyskuje się poprzez stosowanie się do instrukcji dla danej techniki
Pregnant women who experience light-headedness, nausea or feel unwell when they exercise flat on their back should modify their exercise position to avoid the supine position	Kobiety w ciąży, które doświadczają zawrotów głowy, nudności lub złego samopoczucia, gdy ćwiczą leżąc na plecach, powinny zmodyfikować swoją pozycję ćwiczeniową	Kobiety w ciąży, które doświadczają zawrotów głowy, nudności lub złego samopoczucia w trakcie wykonywania ćwiczeń leżąc płasko na plecach powinny unikać wykonywania ich w tej pozycji

V — version; SOGC — Society of Obstetricians and Gynaecologists of Canada; CSEP — Caesarean scar ectopic pregnancy

Reconciliation

At this stage, we compared the two versions (V1 and V2) of the GAQ-P and HCPCF translation point by point. Differences in translation mainly concerned minor linguistic aspects rather than substantive ones. We assumed that the primary user of the instrument would be the general population of pregnant women, *i.e.*, people without medical education. Therefore, as the consensus version (V3), we chose those versions of the translation that were shorter and used more colloquial language.

Back translation

The primary purpose of the backward translation process is to provide a quality-control step demonstrating that the quality of the translation is such that the same meaning can be derived when the translation is moved back into the original language [15]. To implement this stage, we invited two native English speakers who were fluent in Polish. Each independently back-translated the Polish consensus version (V3). This way, we got two English versions of the instrument (Back translation 1 and Back translation 2; Tab. 3 and 4).

Table 3. Summary of results of back translation of the Get Active Questionnaire for Pregnancy from Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the pregnant woman

Consensus on the Polish version (V3)	Back translation 1	Back translation 2	Consensus on the back translation
Kwestionariusz „Bądź aktywna w ciąży"	"Be active in pregnancy" questionnaire	„Be Active During Pregnancy" Questionnaire	"Be active in pregnancy" questionnaire
Imię i nazwisko (+ imię i nazwisko rodzica/opiekuna prawnego, jeśli dotyczy) [PROSZĘ WYPEŁNIĆ DRUKOWANYMI LITERAMI]:	Name and surname (+ name and surname of parent/legal guardian, if applicable) [PLEASE, COMPLETE IN BLOCK CAPITALS]	Full Name (+ Parent/Legal Guardian's Name, if applicable) [PLEASE COMPLETE IN CAPITAL LETTERS]:	Name and surname (+ name and surname of parent/legal guardian, if applicable) [PLEASE, COMPLETE IN BLOCK CAPITALS]
Dzisiejsza data (DD/MM/RRRR):	Date (DD/MM/YYYY)	Today's date (DD/MM/YYYY):	Date (DD/MM/YYYY)
Termin porodu (DD/MM/RRRR):	Due date (DD/MM/YYYY)	Date of delivery (DD/MM/YYYY):	Date of delivery (DD/MM/YYYY):
Tydzień ciąży:	Week of pregnancy:	Week of pregnancy:	Week of pregnancy:
Wiek	Age	Age	Age
Aktywność fizyczna w czasie ciąży ma wiele korzyści zdrowotnych i najczęściej nie wiąże się z ryzykiem ani dla Pani, ani dla Pani dziecka. Jednak w niektórych sytuacjach aktywność fizyczna nie jest zalecana. Ten kwestionariusz ma pomóc Pani w podjęciu decyzji, czy przed rozpoczęciem lub kontynuacją aktywności fizycznej powinna Pani porozmawiać z lekarzem lub położną prowadzącymi ciążę	Physical activity during pregnancy has many health benefits and is usually not risky for you and your baby. However, in some situations, physical activity is not recommended. This questionnaire is intended to help you decide whether you should talk to your obstetric health care provider before starting or continuing physical activity	Being physically active during pregnancy has many health benefits and is usually risk-free for you and your baby. However, in some situations, physical activity is not recommended. This questionnaire is intended to help you decide whether you should talk to your doctor before starting or continuing physical activity	Physical activity during pregnancy has many health benefits and is usually not risky for you and your baby. However, in some situations, physical activity is not recommended. This questionnaire is intended to help you decide whether you should talk to your obstetric health care provider before starting or continuing physical activity
Proszę odpowiedzieć TAK lub NIE na każde pytanie, na tyle, na ile Pani potrafi. Jeśli Pani stan zdrowia zmieni się wraz z przebiegiem ciąży, powinna Pani ponownie wypełnić ten kwestionariusz	Please reply YES or NO to each question as best you can. If your health changes over the course of your pregnancy, you should complete this questionnaire again	Please answer YES or NO to each question as best you can. If your health changes over the course of your pregnancy, you should complete this questionnaire again	Please reply YES or NO to each question as best you can. If your health changes over the course of your pregnancy, you should complete this questionnaire again
Czy w aktualnej ciąży wystąpiły u Pani:	During this pregnancy, have you experienced:	During this pregnancy, have you experienced:	During this pregnancy, have you:
Łagodne, umiarkowane lub ciężkie choroby układu oddechowego lub sercowo-naczyniowego (np. przewlekłe zapalenie oskrzeli)?	Mild, moderate or severe respiratory or cardiovascular diseases (*e.g.*, chronic bronchitis)?	Mild, moderate or severe respiratory or cardiovascular diseases (*e.g.* chronic bronchitis)?	Mild, moderate or severe respiratory or cardiovascular diseases (*e.g.*, chronic bronchitis)?
Padaczka, która nie jest ustabilizowana?	Non-stable epilepsy?	Epilepsy that is not stable?	Non-stable epilepsy?
Cukrzyca typu 1, która nie jest ustabilizowana lub poziom cukru we krwi jest poza zalecanym zakresem?	Type 1 diabetes that is not stable or your blood sugar level is outside the recommended range?	Type 1 diabetes that is not stable or your blood sugar is outside the recommended range?	Type 1 diabetes that is not stable or your blood sugar level is outside the recommended range?
Choroba tarczycy, która nie jest ustabilizowana lub hormony tarczycy określające czynność tarczycy są poza zalecanym zakresem?	Thyroid disease that is not stable or thyroid hormones that determine thyroid function are out of the target range?	Thyroid disease that is not stable or thyroid hormones that determine thyroid function are out of target range?	Thyroid disease that is not stable or thyroid hormones that determine thyroid function are out of the target range?
Zaburzenia odżywiania lub niedożywienie?	Eating disorders or malnutrition?	Eating disorders or malnutrition?	Eating disorders or malnutrition?
Bliźnięta (28 tydzień ciąży lub później)? Lub ciąża trojacza albo liczniejsza ciąża mnoga?	Twins (28th week of gestation or later)? Or triplets or higher multiples?	Twins (28 weeks gestation or later)? Or triplets or higher multiples?	Twins (28th week of gestation or later)? Or triplets or higher multiples?
Niski poziom czerwonych krwinek (niedokrwistość) z objawami zmęczenia i/lub zawrotami głowy?	Low level of red blood cells (anaemia) with symptoms of fatigue and/or dizziness?	Low level of red blood cells (anemia) with symptoms of fatigue and/or dizziness?	Low level of red blood cells (anaemia) with symptoms of fatigue and/or dizziness?
Wysokie ciśnienie tętnicze krwi (stan przedrzucawkowy, nadciśnienie ciążowe lub przewlekłe nadciśnienie, które nie jest ustabilizowane)?	High blood pressure (pre-eclampsia, gestational hypertension, or chronic hypertension that is not stable)?	High blood pressure (pre-eclampsia, gestational hypertension or chronic hypertension that is not stable)?	High blood pressure (pre-eclampsia, gestational hypertension, or chronic hypertension that is not stable)?

→

Table 3. cont. Summary of results of back translation of the Get Active Questionnaire for Pregnancy from Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the pregnant woman

Consensus on the Polish version (V3)	Back translation 1	Back translation 2	Consensus on the back translation
Dziecko, które rośnie zbyt wolno (wewnątrzmaciczne ograniczenie wzrastania płodu)?	Foetus that grows too slowly (intrauterine growth restriction)?	A baby that grows too slowly (intrauterine growth restriction)?	A baby that grows too slowly (intrauterine growth restriction)?
Niewyjaśnione krwawienie z dróg rodnych, pęknięcie błon płodowych lub poród rozpoczęty przed 37 tygodniem ciąży?	Unexplained vaginal bleeding, rupture of membranes or delivery before the 37th week of pregnancy?	Unexplained vaginal bleeding, rupture of membranes or delivery before 37 weeks?	Unexplained vaginal bleeding, rupture of membranes or delivery before the 37th week of pregnancy?
Łożysko, które częściowo lub całkowicie zakrywa szyjkę macicy (łożysko przodujące)?	A placenta that partially or completely covers the cervix (placenta praevia)?	A placenta that partially or completely covers the cervix (placenta praevia)?	A placenta that partially or completely covers the cervix (placenta praevia)?
Niewydolna szyjka macicy?	Weak cervix (incompetent cervix)?	Short cervix (cervical insufficiency)?	Weak cervix (incompetent cervix)?
Szew lub taśma wzmacniająca szyjkę macicy?	Cervical stitch or strengthening tape (cerclage)?	Cervical cerclage?	Cervical stitch or strengthening tape (cerclage)?
Czy w poprzednich ciążach wystąpiły u Pani:	In previous pregnancies, have you experienced:	Have you experienced in previous pregnancies:	In previous pregnancies, have you experienced:
Nawracające poronienia (utrata dziecka przed 20 tygodniem ciąży dwa lub więcej razy z rzędu)?	Recurrent miscarriages (losing a baby before 20th week of pregnancy two or more times in succession)?	Recurrent miscarriages (losing a baby before 20 weeks of pregnancy two or more times in a row)?	Recurrent miscarriages (losing a baby before 20th week of pregnancy two or more times in succession)?
Przedwczesny poród (przed 37 tygodniem ciąży)?	Premature birth (before 37th week of pregnancy)?	Premature birth (before 37 weeks of gestation)?	Premature birth (before 37th week of pregnancy)?
Czy ma Pani inne problemy zdrowotne, które mogą wpływać na Pani zdolność do aktywności fizycznej podczas ciąży? Proszę podać co to za problemy zdrowotne:	Have you any other medical conditions that may affect your ability to exercise during pregnancy? Please specify what health problems that are:	Do you have any other medical conditions that may affect your ability to exercise during pregnancy? Please specify what kind of health problem this is:	Have you any other medical conditions that may affect your ability to exercise during pregnancy? Please specify what health problem that is:
Czy jest jakiś inny powód, dla którego obawia się Pani aktywności fizycznej w czasie ciąży?	Is there any other reason why you are worried about physical activity during pregnancy?	Is there any other reason why you are concerned about physical activity during pregnancy?	Is there any other reason why you are worried about physical activity during pregnancy?
Proszę opisać Pani poziom aktywności fizycznej	Please describe your level of physical activity	Please describe your level of physical activity	Please describe your level of physical activity
W czasie typowego tygodnia, w jakich rodzajach aktywności fizycznej Pani uczestniczy (np. pływanie, spacery, trening oporowy/ ćwiczenia kształtujące poszczególne części ciała joga)?	In what types of physical activity do you participate in a typical week (*e.g.*, swimming, walking, resistance training, yoga)?	During a typical week, what types of physical activity do you participate in (*e.g.* swimming, walking, resistance training, yoga)?	In what types of physical activity do you participate in a typical week (*e.g.*, swimming, walking, resistance training, yoga)?
W odniesieniu do tego samego, typowego tygodnia proszę opisać, jak często i jak długo PRZECIĘTNIE uprawia Pani aktywność fizyczną o niskiej, umiarkowanej lub wysokiej intensywności. Proszę zobaczyć definicje intensywności w ramce poniżej	For that typical week, describe on AVERAGE how often and for how long you engage in light, moderate or vigorous physical activity. Please see intensity definitions in the box below	For the same week, describe on average how often and for how long you engage in light, moderate or vigorous physical activity. Please see intensity definitions in the box below	For the same week, describe on average how often and for how long you engage in light, moderate or vigorous physical activity. Please see intensity definitions in the box below
Przeciętnie:	On average:	On average:	On average:
Na ile była Pani aktywna fizycznie w ciągu sześciu miesięcy przed ciążą?	How physically active were you in the six months before pregnancy?	How active were you in the six months before pregnancy?	How physically active were you in the six months before pregnancy?
Na ile była Pani aktywna fizycznie do tej pory podczas tej ciąży?	How physically active have you been during this pregnancy so far?	How active have you been physically during this pregnancy so far?	How physically active have you been during this pregnancy so far?
Jakie są Pani cele związane z aktywnością fizyczną do końca ciąży?	What are your physical activity aims for the rest of your pregnancy?	What are your fitness goals for the rest of your pregnancy?	What are your physical activity aims for the rest of your pregnancy?
CZĘSTOŚĆ (ile razy w tygodniu)	FREQUENCY (how many times a week)	FREQUENCY (how many times a week)	FREQUENCY (how many times a week)
INTENSYWNOŚĆ (proszę przeczytać definicje poniżej)	INTENSITY (please, read the definitions below)	INTENSITY (please read definitions below)	INTENSITY (please, read the definitions below)

→

Table 3. cont. Summary of results of back translation of the Get Active Questionnaire for Pregnancy from Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the pregnant woman

Consensus on the Polish version (V3)	Back translation 1	Back translation 2	Consensus on the back translation
Czas trwania (ile minut na sesję ćwiczeń)	Duration (how may minutes per exercise session)	Duration (how many minutes per exercise session)	Duration (how may minutes per exercise session)
Aktywność fizyczna o niskiej intensywności: Porusza się Pani, ale bez pocenia się i ciężkiego oddychania, np. chodzenie do sklepu lub lekkie prace w ogrodzie	Low-intensity physical activity: you move around but don't sweat or breathe heavily, *e.g.*, going shopping or light gardening	Low-intensity physical activity: You move around but don't sweat or breathe heavily, such as going to the store or doing light gardening	Low-intensity physical activity: you move around but don't sweat or breathe heavily, *e.g.*, going shopping or light gardening
Aktywność fizyczna o umiarkowanej intensywności: Pani tętno wzrasta i może Pani się pocić lub ciężko oddychać. Może Pani mówić, ale nie może śpiewać, np. szybki marsz	Moderate-intensity physical activity: your heart rate increases and you may sweat or breathe heavily. You can speak but cannot sing, *e.g.*, brisk walking	Moderate-intensity physical activity: Your heart rate increases, and you may sweat or breathe heavily. You can talk, but you cannot sing, *e.g.* brisk walking.	Moderate-intensity physical activity: your heart rate increases and you may sweat or breathe heavily. You can speak but cannot sing, *e.g.*, brisk walking.
Aktywność fizyczna o wysokiej intensywności: Pani tętno znacznie wzrasta, czuje się Pani zgrzana i spocona, nie może Pani powiedzieć więcej niż kilka słów bez robienia przerw na oddech, np. szybka jazda na rowerze stacjonarnym lub bieganie	High-intensity physical activity: your heart rate increases significantly, you feel hot and sweaty, and you can't say more than a few words without pausing for breath; *e.g.*, fast riding a stationary bike or running	High-intensity physical activity: Your heart rate increases significantly, you feel hot and sweaty, and you can't say more than a few words without pausing for breath, such as riding a stationary bike fast or running	High-intensity physical activity: your heart rate increases significantly, you feel hot and sweaty, and you can't say more than a few words without pausing for breath; *e.g.*, fast riding a stationary bike or running
Ogólne zalecenia dotyczące aktywności fizycznej w czasie ciąży	General recommendations for physical activity during pregnancy	General recommendations for physical activity during pregnancy	General recommendations for physical activity during pregnancy
Należy postępować zgodnie z zaleceniami dotyczącymi aktywności fizycznej w czasie ciąży zawartymi w polskich wytycznych PTGiP z 2023 (link) i w kanadyjskich wytycznych z 2019 r. (link)	Follow the recommendations on physical activity during pregnancy in the Polish PTGiP guidelines of 2023 (link) and in the Canadian guidelines of 2019 (link)	Follow the recommendations for physical activity during pregnancy in the Polish PTGiP guidelines from 2023 (link) and in the Canadian guidelines from 2019 (link)	Follow the recommendations on physical activity during pregnancy in the Polish PTGiP guidelines of 2023 (link) and in the Canadian guidelines of 2019 (link)
Kobietom w ciąży zaleca się tygodniowo co najmniej 150 minut aktywności fizycznej o umiarkowanej intensywności (np. trening oporowy/ ćwiczenia kształtujące poszczególne części ciała, szybki marsz, pływanie, prace w ogrodzie), rozłożonej na trzy lub więcej dni w tygodniu. Jeśli planuje Pani wziąć udział w intensywnej aktywności fizycznej lub być aktywną fizycznie na wysokości powyżej 2500 m n.p.m., należy skonsultować się ze swoim lekarzem lub położną prowadzącymi ciążę	Pregnant women should engage in at least 150 minutes of moderate-intensity physical activity (e.g., resistance training, brisk walking, swimming, gardening) spread over three or more days a week. If you plan to engage in vigorous physical activity or be physically active above 2,500 meters above sea level, you should consult your obstetric care provider	Pregnant women are recommended at least 150 minutes of moderate-intensity physical activity (e.g. resistance training, brisk walking, swimming, gardening) spread over three or more days a week. If you plan to engage in strenuous physical activity or be physically active above 2,500 meters above sea level, you should consult your pregnancy physician	Pregnant women are recommended at least 150 minutes of moderate-intensity physical activity (e.g., resistance training, brisk walking, swimming, gardening) spread over three or more days a week. If you plan to engage in vigorous physical activity or be physically active above 2,500 meters above sea level, you should consult your obstetric care provider
Jeśli ma Pani jakiekolwiek pytania dotyczące aktywności fizycznej podczas ciąży, należy skonsultować się z wykwalifikowanym instruktorem lub trenerem ćwiczeń w ciąży lub lekarzem czy położną prowadzącymi ciążę. Może to pomóc upewnić się, że Pani aktywność fizyczna jest bezpieczna i odpowiednia dla Pani	If you have any questions about physical activity during pregnancy, please consult a qualified perinatal exercise specialist or a obstetric health care provider. This can help to ensure that your physical activity is safe and suitable for you	If you have any questions about physical activity during pregnancy, please consult with a qualified perinatal exercise specialist or doctor. This can help make sure your physical activity is safe and suitable for you	If you have any questions about physical activity during pregnancy, please consult a qualified perinatal exercise specialist or a obstetric health care provider This can help to ensure that your physical activity is safe and suitable for you
Oświadczenie	Statement	Declaration	Statement
Zgodnie z moją najlepszą wiedzą, wszystkie informacje podane przeze mnie w tym kwestionariuszu są prawdziwe. Jeśli mój stan zdrowia ulegnie zmianie, wypełnię ten kwestionariusz ponownie	To the best of my knowledge, all information I have provided in this questionnaire is correct. If my health changes, I will complete this questionnaire again	To the best of my knowledge, all information I have provided in this questionnaire is correct. If my health changes, I will complete this questionnaire again	To the best of my knowledge, all information I have provided in this questionnaire is correct. If my health changes, I will complete this questionnaire again

→

Table 3. cont. Summary of results of back translation of the Get Active Questionnaire for Pregnancy from Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the pregnant woman

Consensus on the Polish version (V3)	Back translation 1	Back translation 2	Consensus on the back translation
Odpowiedziałam NIE na wszystkie pytania na stronie 1 Proszę umieścić datę i podpisać poniższe oświadczenie Aktywność fizyczna jest zalecana	I have answered NO to all the questions on page 1 Please sign and date the statement below Physical activity is recommended	I answered NO to all the questions on page 1 Please sign and date the statement below Physical activity is recommended	I have answered NO to all the questions on page 1 Please sign and date the statement below Physical activity is recommended
Odpowiedziałam TAK na jedno lub więcej pytań na stronie 1 i porozmawiam z moim lekarzem lub moją położną prowadzącymi ciążę przed rozpoczęciem lub kontynuowaniem aktywności fizycznej. Aby rozpocząć rozmowę z lekarzem lub położną, można skorzystać z „Formularza konsultacji z lekarzem lub położną w zakresie aktywności fizycznej w ciąży" (link)	I have answered YES to one or more of the questions on page 1 and will talk to my obstetric health care provider before starting or continuing any physical activity. To start a conversation with your obstetric health care provider, you can use the prenatal physical activity healthcare professional consultation form (link)	I answered YES to one or more of the questions on page 1 and will talk to my doctor or midwife before starting or continuing any physical activity. To start a conversation with your doctor, you can use the Prenatal Physical Activity Healthcare Professional Consultation Form (link)	I have answered YES to one or more of the questions on page 1 and will talk to my obstetric health care provider before starting or continuing any physical activity. To start a conversation with your obstetric health care provider, you can use the prenatal physical activity healthcare professional consultation form (link)
Rozmawiałam z moim lekarzem lub położną prowadzącymi ciążę, którzy zalecili mi aktywność fizyczną podczas ciąży. Proszę umieścić datę i podpisać poniższe oświadczenie	I have spoken to my obstetric health care provider who recommended to me physical activity during pregnancy. Please sign and date the statement below	I spoke to my doctor or midwife who advised me to exercise during pregnancy. Please sign and date the statement below	I have spoken to my obstetric health care provider who recommended to me physical activity during pregnancy. Please sign and date the statement below
Imię i nazwisko (Imię i nazwisko rodzica/opiekuna prawnego jeśli dotyczy (PROSZĘ WYPEŁNIĆ DRUKOWANYMI LITERAMI)	Name and surname (name and surname of parent/legal guardian, if applicable) [PLEASE, COMPLETE IN BLOCK CAPITALS]	Name and surname (name and surname of parent/legal guardian, if applicable) [PLEASE, COMPLETE IN BLOCK CAPITALS]	Name and surname (name and surname of parent/legal guardian, if applicable) [PLEASE, COMPLETE IN BLOCK CAPITALS]
Podpis (lub podpis rodzica lub opiekuna prawnego, jeśli dotyczy):	Signature (or signature of parent/legal guardian, if applicable):	Signature (or signature of parent/legal guardian, if applicable):	Signature (or signature of parent/legal guardian, if applicable):
Dzisiejsza data (DD/MM/RRRR):	Date (DD/MM/YYYY):	Date (DD/MM/YYYY):	Date (DD/MM/YYYY):
Numer telefonu (opcjonalnie)	Telephone number (optional)	Telephone number (optional)	Telephone number (optional)
Email (opcjonalnie)	Email (optional)	Email (optional)	Email (optional)

V — version

Revision of back translation

Analyzing the two versions of the back translation, our expert group agreed on the consensus back translation. Next, the project manager and the instrument developer compared the consensus back translation with the original instrument. After this stage, minor discrepencies in meaning between the original and translated documents were idenitifed and corrected. Among others, we found a better wording for "not risky" not to imply that physical activity is "risk-free." We have also extended the term referring to professionals providing obstetric care by using "doctor or midwife in charge of pregnancy" (in the original version, we used only the word "doctor"). This is closer to the term "obstetric care provider," used in the original instrument. We also analyzed other words indicated by the instrument developer to ensure that their equivalents in Polish were adequately selected and used. The final version of the consensus back translation is presented in Tables 3 and 4.

Harmonization

At this stage, the Translation and Cultural Adaptation (TCA) group [15] suggested comparing the back translations of multiple language versions with each other and the original instrument to highlight discrepancies between the original and its derivative translations and to achieve a consistent approach to translation problems. At our current state of knowledge, language versions other than the original English and French of the GAQ-P and HCPCF have already been prepared. Nevertheless, in the available databases of scientific works, English-language reports of their translation have not yet been published.

Cognitive debriefing

As recommended by the TCA group, at the cognitive debriefing stage, the final users of the instrument should be involved to identify any issues that may confuse. It is necessary to assess the level of comprehensibility and cognitive

Table 4. Summary of results of back translation of The Health Care Provider Consultation Form for Prenatal Physical Activity from Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the health care provider

Consensus on the Polish version (V3)	Back translation 1	Back translation 2	Consensus on the back translation
FORMULARZ KONSULTACJI Z LEKARZEM LUB POŁOŻNĄ W ZAKRESIE AKTYWNOŚCI FIZYCZNEJ W CIĄŻY	FORM FOR A CONSULTATION WITH A DOCTOR OR A MIDWIFE REGARDING PHYSICAL ACTIVITY IN PREGNANCY	DOCTOR'S/MIDWIFE'S CONSULTATION FORM REGARDING PHYSICAL ACTIVITY IN PREGNANCY	DOCTOR'S/MIDWIFE'S CONSULTATION FORM REGARDING PHYSICAL ACTIVITY IN PREGNANCY
Pana/Pani pacjentka planuje podjąć lub kontynuować aktywność fizyczną w czasie ciąży. Pacjentka udzieliła odpowiedzi „Tak" na co najmniej jedno pytanie w Kwestionariuszu „Bądź Aktywna w Ciąży", w związku z czym zalecono jej zasięgnięcie Pana/Pani porady	Your patient is planning to start or continue physical activity during pregnancy. The patient answered „Yes" to at least one question in the „Be active in pregnancy" questionnaire Therefore, we recommended that she seek your advice	Your patient plans to start or continue physical activity during pregnancy. The patient answered „Yes" to at least one question in the „Be active while pregnant" questionnaire, therefore she was recommended to seek your advice	Your patient is planning to start or continue physical activity during pregnancy. The patient answered „Yes" to at least one question in the „Be active in pregnancy" questionnaire Therefore, we recommended that she seek your advice
Aktywność fizyczna jest bezpieczna dla większości ciężarnych i niesie ze sobą wiele korzyści zdrowotnych. Jednak niektóre kobiety mogą wymagać dokładnej oceny przed podjęciem aktywności fizycznej w trakcie ciąży	Exercise is safe for most pregnant women and has many health benefits. However, a small number of women may require careful evaluation before undertaking any physical activity during pregnancy	Exercise is safe for most pregnant women and has many health benefits. However, a small number of women may require careful evaluation before undertaking any physical activity during pregnancy	Physical activity is safe for most pregnant women and has many health benefits. However, a small number of women may require careful evaluation before undertaking any physical activity during pregnancy
Zgodnie z polskimi i kanadyjskimi wytycznymi dotyczącymi aktywności fizycznej w ciąży, kobiety ciężarne powinny wykonywać co najmniej 150 minut aktywności fizycznej o umiarkowanej intensywności tygodniowo (patrz następna strona). Ale w niektórych przypadkach występują przeciwwskazania do aktywności fizycznej	According to the Polish and Canadian guidelines for physical activity in pregnancy, pregnant women should undertake at least 150 minutes of moderate-intensity physical activity per week (see next page). But in some cases, there are contraindications to physical activity	In line with the Polish and Canadian guidelines for physical activity in pregnancy, pregnant women should exercise at least 150 minutes of moderate-intensity physical activity per week (see next page). But in some cases, there are contraindications to physical activity	According to the Polish and Canadian guidelines for physical activity in pregnancy, pregnant women should undertake at least 150 minutes of moderate-intensity physical activity per week (see next page). But in some cases, there are contraindications to physical activity
Szczególne obawy pacjentki i/lub wykwalifikowanego instruktora lub trenera ćwiczeń w ciąży:	Specific concerns of the patient and/or qualified pregnancy exercise instructor or trainer	Patient and/or Qualified Exercise Specialist Concerns:	Specific concerns of the patient and/or qualified exercise professional
Aby zapewnić możliwie największe bezpieczeństwo postępowania, kobiecie zaleca się konsultację z Panią/Panem w sprawie aktywności fizycznej podczas ciąży. Prosimy o omówienie z kobietą ewentualnych obaw dotyczących aktywności fizycznej i wskazanie w polu poniżej wszelkich zalecanych modyfikacji:	In order to ensure the greatest possible safety, the woman is advised to consult you regarding physical activity during pregnancy. Please discuss with her any concerns you may have regarding physical activity and indicate any recommended modifications in the boxes below:	To ensure the greatest possible safety of management, the woman is advised to consult you regarding physical activity during pregnancy. Please discuss any concerns you may have regarding physical activity with the woman and indicate any recommended modifications in the box below:	To ensure the greatest possible safety, the woman is advised to consult you regarding physical activity during pregnancy. Please discuss with her any concerns you may have regarding physical activity and indicate any recommended modifications in the boxes below:
Zalecam aktywność fizyczną bez modyfikacji i ograniczeń, zgodnie z polskimi i kanadyjskimi wytycznymi dotyczącymi aktywności fizycznej w ciąży	Physical activity without modifications and limitations, in accordance with the Polish and Canadian guidelines for physical activity in pregnancy	Physical activity without modifications and limitations, in accordance with the Polish and Canadian guidelines for physical activity in pregnancy	Physical activity without modifications and limitations, in accordance with the Polish and Canadian guidelines for physical activity in pregnancy
Zalecam stopniowo zwiększać aktywność fizyczną	Gradually increased physical activity	Gradually increased physical activity	Gradually increased physical activity
Zalecam unikać:	I recommend avoiding:	I recommend avoiding:	I recommend avoiding:
Zalecam włączyć:	I recommend including:	I recommend including:	I recommend including:
W miarę możliwości zalecam nadzór ze strony wykwalifikowanego instruktora lub trenera ćwiczeń w ciąży	I recommend supervision by a qualified pregnancy exercise instructor or trainer, if possible	If possible, I recommend supervision by a qualified exercise specialist	I recommend supervision by a qualified exercise professional, if possible

→

Table 4. cont. Summary of results of back translation of The Health Care Provider Consultation Form for Prenatal Physical Activity from Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the health care provider

Consensus on the Polish version (V3)	Back translation 1	Back translation 2	Consensus on the back translation
Kieruję do fizjoterapeuty w celu diagnostyki w kierunku występowania bólu, dysfunkcji i/lub oceny dna miednicy	I am referring to a physiotherapist for diagnosis for pain, dysfunction and/or pelvic floor assessment	I am referring to a physical therapist for diagnosis of pain, disability and/or pelvic floor assessment	I am referring to a physiotherapist for diagnosis for pain, dysfunction and/or pelvic floor assessment
Inne uwagi:	Other comments:	Other remarks:	Other comments:
Przeciwwskazania bezwzględne	Absolute contraindications	Absolute contraindications	Absolute contraindications
Kobiety ciężarne obciążone tymi dolegliwościami powinny kontynuować aktywność związaną z codziennym życiem, ale nie powinny brać udziału w aktywnościach o umiarkowanej lub wysokiej intensywności:	Pregnant women with these ailments should continue to be active in their daily life, but should not take part in moderate or vigorous physical activity:	Pregnant women with these conditions should continue to be active in their daily life, but should not take part in moderate or vigorous physical activity:	Pregnant women with these conditions should continue to be active in their daily life, but should not take part in moderate or vigorous physical activity:
Pęknięcie błon płodowych	Rupture of the membranes	Rupture of the membranes	Rupture of the membranes
Poród przedwczesny	Premature birth	Premature birth	Premature birth
Niewyjaśnione uporczywe krwawienie z pochwy	Unexplained persistent vaginal bleeding	Unexplained persistent vaginal bleeding	Unexplained persistent vaginal bleeding
Łożysko przodujące po 28 tyg. Ciąży	Placenta previa after 28 weeks of pregnancy	Placenta previa after 28 weeks of pregnancy	Placenta previa after 28 weeks of pregnancy
Stan przedrzucawkowy	Preeclampsia	Preeclampsia	Preeclampsia
Niewydolność cieśniowo-szyjkowa	Isthmus-cervical insufficiency	Cervical insufficiency	Cervical insufficiency
Wewnątrzmaciczne ograniczenie wzrostu płodu	Intrauterine growth restriction of the fetus	Intrauterine growth restriction	Intrauterine growth restriction
Ciąża mnoga liczniejsza niż bliźniacza (np. trojaczki)	Multiple pregnancy more than twin (*e.g.*, triplets)	Multiple preganancy more than twin (*e.g.* triplets)	Multiple pregnancy more than twin (*e.g.*, triplets)
Niewyrównana cukrzyca typu 1	Decompensated type 1 diabetes	Uncontrolled Type I diabetes,	Uncontrolled type I diabetes,
Niewyrównane nadciśnienie	Decompensated hypertension	Uncontrolled hypertension	Uncontrolled hypertension
Niewyrównana choroba tarczycy	Decompensated thyroid disease	Uncontrolled thyroid disease,	Uncontrolled thyroid disease,
Inne poważne zaburzenia sercowo-naczyniowe, oddechowe lub ogólnoustrojowe	Other serious cardiovascular, respiratory or general disorders	Other serious cardiovascular, respiratory or systemic disorder	Other serious cardiovascular, respiratory or systemic disorder
Przeciwwskazania względne	Relative contraindications	Relative contraindications	Relative contraindications
Kobiety ciężarne obciążone tymi dolegliwościami powinny omówić z Panem/Panią korzyści i zagrożenia związane z aktywnością fizyczną. Powinny kontynuować aktywność fizyczną, jednakże, jeśli zasadne, modyfikując ćwiczenia, aby zmniejszyć ich intensywność i/lub czas trwania	Pregnant women with these ailments should discuss with you the benefits and risks of physical activity. They should continue their physical activity, however, if appropriate, modify the exercises to reduce their intensity and/or duration	Pregnant women with these conditions should discuss the benefits and risks of physical activity with you. They should continue their physical activity, however, if appropriate, modify the exercises to reduce their intensity and/or duration	Pregnant women with these conditions should discuss the benefits and risks of physical activity with you. They should continue their physical activity, however, if appropriate, modify the exercises to reduce their intensity and/or duration
Nawracające poronienia	Recurring miscarriages	Recurrent pregnancy loss	Recurrent pregnancy loss
Nadciśnienie ciążowe	Gestational hypertension	Gestational hypertension	Gestational hypertension
W wywiadzie spontaniczny poród przedwczesny	History of spontaneous preterm birth	A history of spontaneous preterm birth	A history of spontaneous preterm birth
Łagodna/umiarkowana choroba układu krążenia lub oddechowego	Mild/moderate cardiovascular or respiratory disease	Mild/moderate cardiovascular or respiratory disease	Mild/moderate cardiovascular or respiratory disease
Objawowa niedokrwistość	Symptomatic anemia	Symptomatic anemia	Symptomatic anemia
Niedożywienie	Malnutrition	Malnutrition	Malnutrition
Zaburzenia odżywiania	Eating disorders	Eating disorders	Eating disorders
Ciąża bliźniacza po 28 tygodniu	Twin pregnancy after 28 weeks	Twin pregnancy after the 28th week	Twin pregnancy after the 28th week

→

Table 4. cont. Summary of results of back translation of The Health Care Provider Consultation Form for Prenatal Physical Activity from Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the health care provider

Consensus on the Polish version (V3)	Back translation 1	Back translation 2	Consensus on the back translation
Inne istotne stany chorobowe	Other significant diseases	Other significant medical conditions	Other significant medical conditions
SOGC/CSEP 2019 KANADYJSKIE WYTYCZNE DOTYCZĄCE AKTYWNOŚCI FIZYCZNEJ W CIĄŻY	SOGC/CSEP 2019 CANADIAN GUIDELINES FOR PHYSICAL ACTIVITY IN PREGNANCY	SOGC/CSEP 2019 CANADIAN GUIDELINE FOR PHYSICAL ACTIVITY THROUGHOUT PREGNANCY	SOGC/CSEP 2019 CANADIAN GUIDELINE FOR PHYSICAL ACTIVITY THROUGHOUT PREGNANCY
Oparte na dowodach wytyczne określają odpowiednią ilość aktywności fizycznej, którą kobiety powinny wykonywać przez całą ciążę, aby wspierać zdrowie własne, płodu i noworodka	Evidence-based guidelines define the appropriate amount of physical activity women should undertake throughout their pregnancy to support maternal, fetal and neonatal health	Evidence-based guidelines define the appropriate amount of physical activity women should perfom throughout their pregnancy to support maternal, fetal and neonatal health	Evidence-based guidelines define the appropriate amount of physical activity women should undertake throughout their pregnancy to support maternal, fetal and neonatal health
Badania wskazują na korzyści zdrowotne i bezpieczeństwo z aktywności fizycznej przez cały okres ciąży zarówno dla matki, jak i dziecka. Aktywność fizyczna jest obecnie postrzegana jako kluczowy element wspierania zdrowej ciąży. Stosowanie się do wytycznych może zmniejszyć ryzyko wystąpienia chorób związanych z ciążą, takich jak depresja, o co najmniej 25%, oraz rozwoju cukrzycy ciążowej, nadciśnienia tętniczego i stanu przedrzucawkowego o 40%	Research shows the health benefits and safety of being active throughout pregnancy for both mother and baby. Physical activity is now seen as a key part of a healthy pregnancy. Adherence to guidelines can reduce the risk of pregnancy-related diseases such as depression by at least 25%, and the development of gestational diabetes, high blood pressure and pre-eclampsia by 40%	Research shows the health benefits and safety of being active throughout pregnancy for both mother and baby. Physical activity is now seen as a key element of maintaining a healthy pregnancy. Adherence to guidelines can reduce the risk of pregnancy-related diseases such as depression by at least 25%, and the development of gestational diabetes, high blood pressure and pre-eclampsia by 40%	Research shows the health benefits and safety of being active throughout pregnancy for both mother and baby. Physical activity is now seen as a key element of maintaining a healthy pregnancy. Adherence to guidelines can reduce the risk of pregnancy-related diseases such as depression by at least 25%, and the development of gestational diabetes, high blood pressure and pre-eclampsia by 40%
Kobiety w ciąży powinny tygodniowo wykonywać co najmniej 150 minut aktywności fizycznej o umiarkowanej intensywności przez co najmniej trzy dni w tygodniu. Ale nawet jeśli nie osiągną tego celu, należy je zachęcać do jakiejkolwiek aktywności każdego dnia. Wytyczne zawierają sześć zaleceń:	Pregnant women should undertake at least 150 minutes of moderate-intensity physical activity per week for at least three days per week. But even if they do not achieve this goal, they should be encouraged to do some activity every day. The guidelines contain six recommendations:	Pregnant women should engage in at least 150 minutes of moderate-intensity physical activity per week for at least three days per week. But even if they do not achieve this goal, they should be encouraged to do any activity every day. The guidelines contain six recommendations:	Pregnant women should undertake at least 150 minutes of moderate-intensity physical activity per week for at least three days per week. But even if they do not achieve this goal, they should be encouraged to do some activity every day. The guidelines contain six recommendations:
Wszystkie kobiety bez przeciwwskazań powinny być aktywne fizycznie przez cały okres ciąży. Zbadano poszczególne podgrupy: • kobiety, które wcześniej były nieaktywne • kobiety ze zdiagnozowaną cukrzycą ciążową • kobiety z nadwagą lub otyłością (wskaźnik masy ciała sprzed ciąży ≥ 25 kg/m^2)	All women without contraindications should be physically active throughout pregnancy. Specific subgroups were examined: • previously inactive women • women diagnosed with gestational diabetes • women who are overweight or obese (pre-pregnancy body mass index ≥ 25 kg/m^2)	All women without contraindications should be physically active throughout pregnancy. Individual subgroups were examined: • women who were previously inactive • women diagnosed with gestational diabetes • women who are overweight or obese (pre-pregnancy body mass index ≥ 25 kg/m^2)	All women without contraindications should be physically active throughout pregnancy. Specific subgroups were examined: • women who were previously inactive • women diagnosed with gestational diabetes • women who are overweight or obese (pre-pregnancy body mass index ≥ 25 kg/m^2)
Kobiety w ciąży powinny tygodniowo poświęcać co najmniej 150 minut na aktywność fizyczną o umiarkowanej intensywności, aby osiągnąć klinicznie znaczące korzyści zdrowotne i zmniejszyć częstość występowania powikłań ciążowych	Pregnant women should spend at least 150 minutes per week on moderate-intensity physical activity to achieve clinically significant health benefits and reduce the incidence of pregnancy complications	Pregnant women should spend at least 150 minutes per week of moderate-intensity physical activity to achieve clinically significant health benefits and reduce the incidence of pregnancy complications	Pregnant women should spend at least 150 minutes per week on moderate-intensity physical activity to achieve clinically significant health benefits and reduce the incidence of pregnancy complications
Aktywność fizyczna powinna być wykonywana przez co najmniej trzy dni w tygodniu; jednakże zaleca się jej podejmowanie każdego dnia	Physical activity should be performed at least three days a week; however, it is encouraged to undertake it every day	Physical activity should be performed at least three days a week; however, it is encouraged to do so every day	Physical activity should be performed at least three days a week; however, it is encouraged to undertake it every day

→

Table 4. cont. Summary of results of back translation of The Health Care Provider Consultation Form for Prenatal Physical Activity from Polish according to International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) recommendations — to be completed by the health care provider

Consensus on the Polish version (V3)	Back translation 1	Back translation 2	Consensus on the back translation
Kobiety w ciąży powinny wykonywać różnorodne ćwiczenia pobudzające układ krążeniowo-oddechowy i wzmacniające poszczególne grupy mięśniowe, by osiągnąć większe korzyści. Korzystne może być również uprawianie jogi i/lub wykonywanie ćwiczeń rozciągających	Pregnant women should engage in a variety of aerobic and strengthening exercises to obtain greater benefits. It may also be beneficial to practice yoga and/or perform stretching exercises	Pregnant women should engage in a variety of aerobic and strengthening exercises to obtain greater benefits. It may also be beneficial to practice yoga and/or perform stretching exercises	Pregnant women should engage in a variety of aerobic and strengthening exercises to obtain greater benefits. It may also be beneficial to practice yoga and/or perform stretching exercises
Trening mięśni dna miednicy (np. tzw. ćwiczenia Kegla) można wykonywać codziennie, aby zmniejszyć ryzyko nietrzymania moczu. W celu uzyskania optymalnych korzyści zaleca się instruktaż odpowiedniej techniki ich wykonywania	Pelvic floor muscle training (*e.g.*, Kegel exercises) can be done daily to reduce the risk of urinary incontinence. In order to obtain the best benefits, it is recommended to teach the appropriate technique	Pelvic floor muscle training (*e.g.* Kegel exercises) can be done daily to reduce the risk of urinary incontinence. To obtain the best benefits, it is recommended to be instructed in appropriate techniques	Pelvic floor muscle training (*e.g.*, Kegel exercises) can be done daily to reduce the risk of urinary incontinence. To obtain the best benefits, it is recommended to teach the appropriate technique
Kobiety w ciąży, które doświadczają zawrotów głowy, nudności lub złego samopoczucia w trakcie ćwiczeń leżąc płasko na plecach, powinny unikać wykonywania ich w tej pozycji	Pregnant women who experience dizziness, nausea or discomfort while lying flat on their backs should avoid exercising in this position	Pregnant women who experience dizziness, nausea, or malaise while lying flat on their backs should avoid exercising in this position	Pregnant women who experience dizziness, nausea or discomfort while lying flat on their backs should avoid exercising in this position

V — version; SOGC — Society of Obstetricians and Gynaecologists of Canada; CSEP — Caesarean scar ectopic pregnancy

equivalence of the translation. We completed this stage in the period from February to June 2023. We used an online survey form in which the respondents assessed each item from the GAQ-P and HCPCF and the answer options. The goal of the survey was to obtain feedback on the clarity and cultural appropriateness of the translation. Respondents were also asked for suggestions if they thought the text needed improvement or clarification. Responses from 70 stakeholders were received (they could represent more than one of the following groups): pregnant or postpartum women (n = 23; 33%); doctors and midwives (n = 4; 6%); exercise professionals and physiotherapists (n = 37; 53%); students of related field of study (n = 7; 10%), psychologists (n = 1; 1%); dietitians (n = 1; 1%), public health specialists (n = 1; 1%), others (n = 2; 3%). The vast majority of respondents considered the wording of the questions and the text in the questionnaire understandable. A few proposed minor changes or additions.

The questionnaire (V3) was also discussed several times during stakeholder meetings, including educational events for pregnant women and training on physical activity in pregnancy addressed to exercise professionals, physiotherapists, and obstetric care providers. The assessment of the instrument needed to be more structured here. The participants in the cognitive debriefing stage were native Polish speakers and residents of Poland. In addition to assessing the comprehensibility of the instrument, the stakeholders confirmed the need for its implementation in the Polish market.

Revision of debriefing results

According to the TCA group, a review of the cognitive debriefing results against the original version of the instrument is the key to ensuring cultural relevance. In July 2023, the project manager reviewed the outcomes of the online survey and identified parts of the translation requiring improvement. The changes were approved by the expert group and by the instrument developer. We have marked them in italics in Tables 3 and 4.

Proofreading

A few minor changes to the questionnaires were made to ensure proper grammar. These final adaptations were reviewed and approved by the group of experts involved in the Polish translation. The final Polish verisions are presentented in supplementary materials: the GAQ-P (Kwestionariusz "Bądź aktywna w ciąży") as supplementary file 1 [16] and the HCPCF (Formularz konsultacji z lekarzem lub położną w zakresie aktywnosci fizycznej w ciąży) as supplementary file 2 [17].

Final report

The last step was to describe the individual stages of all translation and cultural adaptation process. According to the

assumptions of the TCA group, this aimed to facilitate future translations of GAQ-P and HCPCF into other languages and its adaptations to different cultures, and to enable the transfer of our experience to other translation processes of similar instruments [15].

DISCUSSION

This paper describes the translation and cross-cultural adaptation of the Get Active Questionnaire for Pregnancy, and the Health Care Provider Consultation Form for Prenatal Physical Activity into Polish. Following broad consultation on this work, respondents from key target users indicated that the translations were clear and culturally appropriate. Respondents also emphasized the need for widespread knowledge translation (*i.e.*, educational events, presentation at scientific conferences) to enhance awareness of these tools and reduce barriers to physical activity in pregnant Polish women. Considering that about half of Polish women are physically inactive during pregnancy [8], this opinion is justified.

Historically, all pregnant women were advised to speak to their obstetric care provider about whether or not it was advisable to be physically active during pregnancy. This created a significant barrier to physical activity participation, and with high-quality evidence supporting the safety and health benefits for pregnant women is no longer warranted. However, identifying the small number of women who may develop a contraindication to exercise during pregnancy is essential. The GAQ-P was designed to be self-completed by pregnant women for this purpose. Answering individual questions, they are able to easily self-assess their health, the course of pregnancy and the level and quality of physical activity undertaken so far, both during and before pregnancy. Based on their responses to these questions, they will have a clear direction that they are at low risk for contraindication to prenatal physical activity and can begin or continue physical activity, or they will be directed to obtain additional screening with their obstetric care provider. Additionally, the short evidence-based information contained in the questionnaire may reinforce their positive health behaviours, thus possibly contributing to raising the level of PAP in Polish population. Certainly, this assumption would require verification in research in the coming years.

The second part of the instrument, the HCPCF, is designed as a communication tool between health care providers, pregnant women and (if appropriate), exercise professionals. If a woman completes the first part of the instrument responds "yes" to any questions (indicating she may have a contraindication), the HCPCF provides health professionals with a structured interview scenario. It is intended to idenfity the presence or absence of relative or absolute contraindications. In some cases, physical activity may continue without modification, while in others, modification to the intensity, duration and or modality of the activity may be recommended. Nevertheless, it should be emphasized that daily activity and low-intensity exercise are still recommended for most pregnancy complications [18]. Organizations in the field of gynaecology and obstetrics advise against referring patients to the so-called "bed rest" and total restriction of physical activity [19]. Such a clinically unsupported recommendation is considered an unethical behaviour towards the patient due to the health-damaging consequences of physical inactivity [20]. It may also result in worse newborn outcomes [21].

Due to common unjustified opinions about the supposedly harmful effects of physical activity on the course of pregnancy, the promotion of PAP can be difficult. However, a study of more than 9,000 Polish women, the authors observed that women who were informed by gynaecologists about the beneficial influence of PAP exercised significantly more often than those who did not receive such information [8]. Yet, over 85% of Polish obstetric care providers either did not address the issue of PAP with the future mothers or recommended its restriction [22]. This low rate of counselling on the benefits of PAP has been attributed to a lack of specialist knowledge to promote PAP. Therefore, it is necessary to implement educational training for obstetric care providers on this subject using the recently published Polish guidelines [6]. Malta et al. [23] indicated that after an educational intervention health care professionals were almost three times more likely to give their pregnant patients proper guidance regarding physical activity than the control group without educational support. Tools such as the GAQ-P and HCPCF will further enhance educational opportunities and knowledge translation.

Separating professional competencies in promoting, planning, and implementing physical activity programs is crucial [24]. Obstetric care providers should carefully evaluate women with medical or obstetric complications. They should also provide them with general information about the benefits of PAP and the risks of physical inactivity. In contrast, the design and implementation of exercise programmes are tasks for exercise professionals. The effectiveness of the exercise programme is determined by the appropriate interaction of its major components: intensity, duration, frequency, type, and progression. In working with a pregnant woman, one should also ensure that the exercises address her special needs as an expectant mother [24]. In the HCPCF, obstetric care providers can recommend supervision by a Qualified Exercise Professional to their pregnant patients. To accomplish this task, it is essential that instructors, trainers, coaches, other exercise specialists,

and physiotherapists are competent and trustworthy. It is best that their vocational training takes place in reliable institutions that ensure high quality of education, *e.g.*, in line with the European educational standards [25]. In Poland, it is best for professional qualifications to be confirmed in accordance with the Integrated Qualifications System [26]. Due to the fact that more and more women, including female athletes, want to continue sports activities of vigorous and high intensity during pregnancy [27], exercise professionals should also have specialist competencies in this area. The Polish qualifications for performing these professional tasks are "The instructor of exercises in uncomplicated pregnancy" [28] and "The trainer of pregnant and postpartum athletes" [29].

The strength of this work is that the original version of the GAQ-P and HCPCF were developed in a multi-stage, rigorous process led by the instrument developer [13]. Therefore, the legitimacy of both the structure of the questionnaires and their content have been reliably confirmed. The methodology proposed by the TPA group provided us with a structured and transparent process of translation and cultural adaptation [14]. Doubts may be raised to what extent theses tools will be introduced to the Polish market and to what extent they will be widely used by pregnant women, obstetric care providers, and exercise professionals. Certainly, extensive promotional and educational activities in this regard should be planned.

CONCLUSIONS

Target users have positively evaluated the Polish version of GAQ-P and HCPCF. Thanks to the ISPOR methodology, we have obtained a trustworthy, evidence-based screening tool. It should support obstetric care providers in identifying pregnant patients who may not benefit from moderate to vigorous physical activity. At the same time, the GAQ-P can reduce the barriers for most women who should and are willing to be physically active during pregnancy. The usefulness of this instrument and the degree of its implementation on the Polish market should be assessed in future works.

Article information and declarations

Funding

This work was developed as part of the NEPPE project: 'The New Era of Pre- and Postnatal Exercise — training for instructors and trainers of various forms of physical activity in the field of online provision of exercise for pregnant and postpartum women', financially supported by the Polish National Academic Exchange Agency (NAWA) within the SPINNAKER programme (No. PPI/SPI/2020/1/00082/DEC/02), run at the Gdansk University of Physical Education and Sport, Poland in 2021–2023.

Acknowledgements

The authors would like to thank the CSEP for allowing us to translate the instrument, and all stakeholders who volunteered for the Cognitive Debriefing stage of the translation process.

Conflict of interest

The authors declare that there are no conflicts of interest.

Supplementary material

Supplementary File 1. Get Active Questionnaire for Pregnancy (GAQ-P) — polish.

Supplementary File 2. Get Active Questionnaire for Pregnancy (GAQ-P) Health Care Provider (HCP) consultation form — polish.

REFERENCES

1. Bø K, Artal R, Barakat R, et al. Exercise and pregnancy in recreational and elite athletes: 2016 evidence summary from the IOC expert group meeting, Lausanne. Part 1-exercise in women planning pregnancy and those who are pregnant. Br J Sports Med. 2016; 50(10): 571–589, doi: 10.1136/bjsports-2016-096218, indexed in Pubmed: 27127296.
2. Bø K, Artal R, Barakat R, et al. IOC Medical Commission. Exercise and pregnancy in recreational and elite athletes: 2016 evidence summary from the IOC expert group meeting, Lausanne. Part 2-the effect of exercise on the fetus, labour and birth. Br J Sports Med. 2016; 50(21): 1297–1305, doi: 10.1136/bjsports-2016-096810, indexed in Pubmed: 27733352.
3. Bø K, Artal R, Barakat R, et al. IOC Medical Commission. Exercise and pregnancy in recreational and elite athletes: 2016/17 evidence summary from the IOC Expert Group Meeting, Lausanne. Part 3-exercise in the postpartum period. Br J Sports Med. 2017; 51(21): 1516–1525, doi: 10.1136/bjsports-2017-097964, indexed in Pubmed: 28642221.
4. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020; 54(24): 1451–1462, doi: 10.1136/bjsports-2020-102955, indexed in Pubmed: 33239350.
5. Szumilewicz A, Worska A, Santos-Rocha R, et al. Evidence-Based and Practice-Oriented Guidelines for Exercising During Pregnancy. Exercise and Physical Activity During Pregnancy and Postpartum. 2022: 177–217, doi: 10.1007/978-3-031-06137-0_7.
6. Kwiatkowska E, Kajdy A, Sikora-Szubert A, et al. Polish Society of Gynecologists and Obstetricians (PTGiP) and Polish Society of Sports Medicine (PTMS) recommendations on physical activity during pregnancy and the postpartum period. Ginekol Pol. 2023 [Epub ahead of print], doi: 10.5603/GP.a2023.0080, indexed in Pubmed: 37599577.
7. Szatko A, Kacperczyk-Bartnik J, Bartnik P, et al. Physical activity during pregnancy - the state of Polish women's knowledge. Ginekol Pol. 2021; 92(11): 804–811, doi: 10.5603/GP.a2021.0050, indexed in Pubmed: 33914330.
8. Walasik I, Kwiatkowska K, Kosińska Kaczyńska K, et al. Physical Activity Patterns among 9000 Pregnant Women in Poland: A Cross-Sectional Study. Int J Environ Res Public Health. 2020; 17(5), doi: 10.3390/ijerph17051771, indexed in Pubmed: 32182850.
9. Wojtyła A, Kapka-Skrzypczak L, Paprzycki P, et al. Epidemiological studies in Poland on effect of physical activity of pregnant women on the health of offspring and future generations - adaptation of the hypothesis development origin of health and diseases. Ann Agric Environ Med. 2012; 19(2): 315–326, indexed in Pubmed: 22742808.
10. Davenport MH, Meah VL, Ruchat SM, et al. Prenatal exercise is not associated with fetal mortality: a systematic review and meta-analysis. Br J Sports Med. 2019; 53(2): 108–115, doi: 10.1136/bjsports-2018-099773, indexed in Pubmed: 30337346.
11. Davenport MH, Meah VL, Ruchat SM, et al. Impact of prenatal exercise on neonatal and childhood outcomes: a systematic review and me-

ta-analysis. Br J Sports Med. 2018; 52(21): 1386–1396, doi: 10.1136/bjsports-2018-099836, indexed in Pubmed: 30337465.
12. Regulation of the Ministry of Health of August 16, 2018 on the organizational standard of perinatal care (Journal of Laws of 2018, item 1756.
13. Davenport MH, Neil-Sztramko S, Lett B, et al. Development of the Get Active Questionnaire for Pregnancy: breaking down barriers to prenatal exercise. Appl Physiol Nutr Metab. 2022; 47(7): 787–803, doi: 10.1139/apnm-2021-0655, indexed in Pubmed: 35442812.
14. Bgeginski R, DeSousa DA, Barroso BM, et al. Psychometric Properties of the Brazilian Portuguese Version of the PARmed-X for Pregnancy. J Phys Act Health. 2017; 14(8): 646–651, doi: 10.1123/jpah.2016-0477, indexed in Pubmed: 28422553.
15. Wild D, Grove A, Martin M, et al. ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005; 8(2): 94–104, doi: 10.1111/j.1524-4733.2005.04054.x, indexed in Pubmed: 15804318.
16. Kwestionariusz bądź aktywna w ciąży. GAQ-P-Polish. csep.ca (11.12.2023).
17. Formularz konsultacji z lekarzem lub położną w zakresie aktywności fizycznej w ciąży. GAQ-P-HCP-Consultation-Form-Polish.pdf. csep.ca (11.12.2023).
18. Meah VL, Davies GA, Davenport MH. Why can't I exercise during pregnancy? Time to revisit medical 'absolute' and 'relative' contraindications: systematic review of evidence of harm and a call to action. Br J Sports Med. 2020; 54(23): 1395–1404, doi: 10.1136/bjsports-2020-102042, indexed in Pubmed: 32513676.
19. Physical Activity and Exercise During Pregnancy and the Postpartum Period: ACOG Committee Opinion, Number 804. Obstet Gynecol. 2020; 135(4): e178–e188, doi: 10.1097/AOG.0000000000003772, indexed in Pubmed: 32217980.
20. McCall CA, Grimes DA, Lyerly AD. "Therapeutic" bed rest in pregnancy: unethical and unsupported by data. Obstet Gynecol. 2013; 121(6): 1305–1308, doi: 10.1097/AOG.0b013e318293f12f, indexed in Pubmed: 23812466.
21. Matenchuk B, Khurana R, Cai C, et al. Prenatal bed rest in developed and developing regions: a systematic review and meta-analysis. CMAJ Open. 2019; 7(3): E435–E445, doi: 10.9778/cmajo.20190014, indexed in Pubmed: 31289044.
22. Wojtyła C, Ciebiera M, Wojtyła-Buciora P, et al. Physical activity patterns in third trimester of pregnancy - use of pregnancy physical activity questionnaire in Poland. Ann Agric Environ Med. 2020; 27(3): 388–393, doi: 10.26444/aaem/110480, indexed in Pubmed: 32955220.
23. Malta MB, Carvalhaes MA, Takito MY, et al. Educational intervention regarding diet and physical activity for pregnant women: changes in knowledge and practices among health professionals. BMC Pregnancy Childbirth. 2016; 16(1): 175, doi: 10.1186/s12884-016-0957-1, indexed in Pubmed: 27439974.
24. Santos-Rocha R, Fernandes de Carvalho M, Prior de Freitas J, et al. Active Pregnancy: A Physical Exercise Program Promoting Fitness and Health during Pregnancy-Development and Validation of a Complex Intervention. Int J Environ Res Public Health. 2022; 19(8), doi: 10.3390/ijerph19084902, indexed in Pubmed: 35457769.
25. Santos-Rocha R, Pajaujiene S, Szumilewicz A. ACTIVE PREGNANCY: Workshop on Promotion of Physical Activity in Pregnancy for Exercise Professionals. J Multidiscip Healthc. 2022; 15: 2077–2089, doi: 10.2147/JMDH.S370453, indexed in Pubmed: 36128597.
26. The Act of December 22, 2015 on the Integrated Qualification System (Journal of Laws of 2015, item 64; Journal of Laws of 2020, item 226.
27. Szumilewicz A, Santos-Rocha R, Worska A, et al. How to HIIT while pregnant? The protocol characteristics and effects of high intensity interval training implemented during pregnancy – A systematic review. Baltic Journal of Health and Physical Activity. 2021; 14(1): Article-1, doi: 10.29359/bjhpa.14.1.01.
28. Announcement of the Minister of Sport and Tourism of August 10, 2023 on the inclusion of the market qualification "Conducting exercises for women in uncomplicated pregnancy" to the Integrated Qualifications System. Polish Monitor. Item 913. Official Journal of the Republic of Poland 2023.
29. Announcement of the Minister of Sport and Tourism of January 4, 2023 on the inclusion of the market qualification "Conducting the training process for pregnant and postpartum athletes" to the Integrated Qualifications System. Polish Monitor. Item 164. Official Journal of the Republic of Poland 2023.

VIA MEDICA

CLINICAL VIGNETTE

Ginekologia Polska
2024, vol. 95, no. 6, 502–503

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/gpl.96927

Vulvar Merkel cell carcinoma combined with squamous cell carcinoma of the vulva

Marlena Cwynar[1, 2], Ewa Chmielik[3], Grzegorz Cwynar[2], Piotr Ptak[1, 2], Karolina Kowalczyk[1]

[1]*Department of Endocrinological Gynecology, Faculty of Medicine in Katowice, Medical University of Silesia, Poland*

[2]*Department of Gynecology and Gynecological Oncology, Hospital in Czeladz, Poland*

[3]*Tumor Pathology Department, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland*

We present a case of a 67-year-old woman who was admitted to the department of gynecological oncology with a complaint of persistent and mild pain in the area of the left labia minora. The patient has been treated with antibiotics and anti-inflammatory drugs with no improvement. She also had a dermatological consultation; however, it did not reveal dermatological causes of the patient's complaints nor any other abnormal skin lesions. A suggestion of a persistent Bartholin's gland abscess has been made. Hence, she has been referred to the surgical removal of the lesion. The general condition of the patient was stable. She reported no additional gynecologic, gastrointestinal symptoms, rapid weight loss or any other complaints.

Physical examination revealed a palpable nodular lesion about 3 cm large in the area of the left labia minora. A mild bloody discharge in the vagina was also detected. Inguinal as well as other palpable lymph nodes were not enlarged. There were no significant abnormalities on the skin of the vulva or in the transvaginal ultrasound. The abdominal ultrasound has shown no abnormalities. The patient was qualified for surgical removal of the lesion.

The oval, solid, smooth-surface tumor approximately 4 cm large has been removed during the surgery. The recovery period was uneventful, and the patient was discharged after two days. A definitive histopathological diagnosis revealed neuroendocrine neoplasm (NEN) combined with squamous cell carcinoma (SCC). Immunohistochemically, cells of NEN expressed characteristic immunophenotype: synaptophysin(+), CK7(+), CK20(+) CD56(+) whereas the squamous part was p63 (+) (Fig. 1). The microscopic morphology of NEN corresponded to Merkel cell carcinoma (MCC). Based on immunohistochemistry, primary MCC combined with SCC (MCC/SCC) of the vulva was signed. Positive surgical margins were detected. The patient has been referred to adjuvant radio-chemotherapy. Unfortunately, the patient did not return for follow-up.

NENs are rare tumors arising mainly in pancreas, lungs, and gastrointestinal tract [1]. They are rarely encountered in the gynecologic tract and constitute < 2% of female reproductive tumors. NEN of the vulva accounts for < 1% of cases. Commonly, they are admixed with other histological types, most frequently SCC [2]. Currently, WHO has divided NENs to well-differentiated neuroendocrine tumours and poorly differentiated neuroendocrine carcinomas (NECs). NECs subdivide to small-cell NECs, large-cell NECs and carcinomas admixed with NEC. This WHO classification is uniformal for NENs at majority locations, including female genital tract. However, current division has not comprised MCC [3, 4].

MCC is an aggressive, primary cutaneous neuroendocrine carcinoma, characterized by coexpression of neuroendocrine markers and CK20 (a discriminant from other types of visceral NENs) [5]. Most commonly MCC develops in elderly patients in the sun-exposed skin areas, where its occurrence is usually related to Merkel cell polyomavirus (MCV) [3, 5]. MCCs, with or without SCC component, are extremely rare in the gynecological area [1, 5].

Vulvar MCC coexistence with SCC might indicate the role of HPV in the pathogenesis of this neoplasm. The previous study determined both malignant components of the vulva incorporated the same high-risk HPV-DNA in their genome, without MCV genome. The lack of the TP53 mutation, which is related to ultraviolet light damage, was also detected.

Corresponding author:
Karolina Kowalczyk
Department of Gynecological Endocrinology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland
e-mail: karolina.kowalczyk74@gmail.com

Received: 11.08.2023 Accepted: 19.09.2023 Early publication date: 23.09.2023

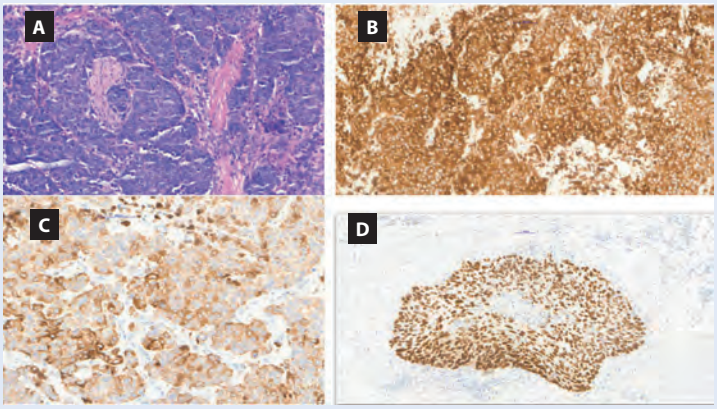


Figure 1. Vulvar Merkel cell carcinoma combined with squamous cell carcinoma. **A.** Tumor histopathology with neural invasion, hematoxylin & eosin stain, 29.56×; **B.** Neuroendocrine differentiation — diffuse synatophysin expression, immunohistochemistry stain (IS), 30.24×; **C.** Cytokeratin 20, IS, 45.79×; **D.** p63 expression in a focus of squamous cell carcinoma, IS, 26.33×

These findings support the suspicion that a vulvar MCC is HPV-related, whereas in the other origin it is more akin to be MCV-related [5].

The diagnostic process requires the assays for a possible primary lesion, as well as secondary metastases. In the presented case, based on dermatological consultation, imaging and clinical examinations, no primary lesion in the other location has been diagnosed. There are no specific guidelines regarding treatment. In clinical practices surgical excision plays a pivotal role in early-stage cases followed by adjuvant radiation or chemoradiation. Some patients might benefit from immunotherapy as well [1, 2].

We want to draw attention to the possibility of MCC (with or without SCC component) of the vulva, the importance of proper approach to the differential diagnosis and further follow-up of the patient in order to diagnose secondary metastasis. Moreover, we want to highlight the value of prophylactic vaccination against oncogenic HPV, not only to prevent anogenital SCC, but also HPV-associated vulvar MCC.

Article information and declarations

Ethics statement

Written informed consent for publication was obtained from the patient.

Author contributions

The authors confirm sole responsibility for the following: Marlena Cwynar: study conception and design; Ewa Chmielik: analysis and interpretation of results; Grzegorz Cwynar: data collection; Piotr Ptak: data collection; Karolina Kowalczyk: manuscript preparation.

Acknowledgments

None.

Conflict of interest

There are no conflicts of interest.

Funding

None.

Supplementary material

None.

REFERENCES

1. Georgescu TA, Bohiltea RE, Munteanu O, et al. Emerging Therapeutic Concepts and Latest Diagnostic Advancements Regarding Neuroendocrine Tumors of the Gynecologic Tract. Medicina (Kaunas). 2021; 57(12), doi: 10.3390/medicina57121338, indexed in Pubmed: 34946283.
2. Virarkar M, Vulasala SS, Morani AC, et al. Neuroendocrine Neoplasms of the Gynecologic Tract. Cancers (Basel). 2022; 14(7), doi: 10.3390/cancers14071835, indexed in Pubmed: 35406607.
3. Neuroendocrine neoplasia in WHO Classification of Tumours Editorial Board. Female genital tumours. International Agency for Research on Cancer, Lyon (France) 2020.
4. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol. 2008; 58(3): 375–381, doi: 10.1016/j.jaad.2007.11.020, indexed in Pubmed: 18280333.
5. Lingamaneni P, Vohra I, Upadhyay S, et al. 1402 Metastatic Merkel Cell Carcinoma With Isolated Pancreatic Metastases. American Journal of Gastroenterology. 2019; 114(1): S777–S777, doi: 10.14309/01.ajg.0000595136.60337.25.

VIA MEDICA

CLINICAL VIGNETTE

Ginekologia Polska
2024, vol. 95, no. 6, 504–505

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/gpl.96875

Misleading diagnosis in a pregnant patient — ruptured metastatic choriocarcinoma mimicking liver hemangiomas treated with emergency embolization

Maciej Szmygin[1], Sara Moqbil[2], Radzislaw Mierzynski[3], Bozena Leszczynska-Gorzelak[3], Krzysztof Pyra[4]

[1]Department of Interventional Radiology and Neuroradiology, Medical University of Lublin, Poland
[2]Students' Scientific Society at the Department of Interventional Radiology and Neuroradiology, Medical University of Lublin, Poland
[3]Chair and Department of Obstetrics and Perinatology, Medical University of Lublin, Poland
[4]Department of Interventional Radiology and Neuroradiology, Medical University of Lublin, Poland

Choriocarcinomas are highly vascular neoplasms mostly arising from an abnormal trophoblast that can occur at any time during or after any type of gestation [1]. Metastases are very frequent and lungs, liver and brain are the most common organs of the disease's spread outside of the pelvis. Due to the wide variety of clinical presentations in metastatic choriocarcinoma, the accurate diagnosis is challenging and can easily be missed as the cancer mimics lots of other medical conditions. We present the case of a multigravida patient whose metastatic choriocarcinoma was initially misdiagnosed because of a seemingly obvious explanation in imaging examination.

A 24-year-old female patient in 29th week of her second pregnancy was admitted due to pain under the right breast. Her first pregnancy terminated in term by vaginal delivery six years prior to the admission. No abnormalities were found on gynecological examination. Abdominal Ultrasound demonstrated the presence of numerous well-defined hyperechoic lesions in the liver. Diagnosis of hepatic haemangiomatosis was made and analgetic treatment was initiated. Despite the treatment, the clinical condition of the patient deteriorated and she developed symptoms of hypovolemic shock most probably due to the rupture of the hepatic lesions. It was decided to terminate the pregnancy by cesarean section, perform laparotomy and embolize the ruptured hemangiomas. She underwent emergency cesarean section with intraoperative uterine sampling. During laparotomy the liver ruptures were surgically repaired and because of the bleeding from the spleen the splenectomy and surgical perihepatic packing were also performed. The female neonate weighed 1560 g with Apgar scores of 2 and 6 at 1 and 5 min, respectively. Afterwards, the endovascular procedure was performed from the femoral access. A pathological vascular bed of a clinically known hemangioma in the segment II/III of the liver with visible active extravasation of contrast agent was visualized. Embolization was performed using a mixture of gleubran glue and lipiodol. Complete exclusion of blood supply to the lesions was confirmed in control angiography (Fig. 1).

A post-operative computed tomography disclosed numerous foci with contrast enhancement typical of hemangiomas. A chest X-ray showed the presence of further foci located subpleurally and in the middle fields of the upper lungs. Subsequent imaging studies confirmed the build-up of fluid in the right pleural cavity. The laboratory tests showed an elevated level of bHCG (131000 mIU/mL) — based on these findings, metastatic choriocarcinoma was suspected. The diagnosis was confirmed by the histological-pathological examination.

The patient was admitted to the Intensive Care Unit unconscious, under sedation, intubated, with artificial lung ventilation. After transfusion of the blood products, the patient's condition improved and artificial lung ventilation was terminated. On the 6th day after caesarean section, due to repeated bleeding from the liver lesions, the patient was again qualified for embolization and laparotomy. Afterwards, the patient revived EMA-CO (etoposide, methotrexate, actinomycin

Corresponding author:
Maciej Szmygin
Department of Interventional Radiology and Neuroradiology, Medical University of Lublin, Jaczewskiego 8 Str., 20–090 Lublin, Poland; phone: 0048509679033
e-mail: mszmygin@gmail.com

Received: 8.08.2023 Accepted: 13.12.2023 Early publication date: 22.01.2024

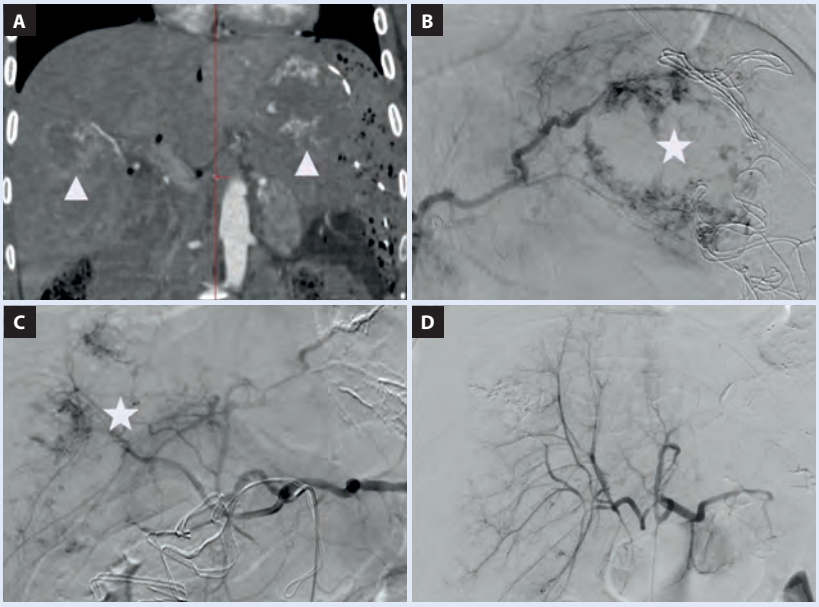


Figure 1. A. Post-operative computed tomography showing numerous intrahepatic foci with contrast enhancement typical of hemangiomas (white triangles); **B, C.** Digital subtraction angiography (DSA) examination showed pathological vascular beds in the liver with visible active extravasation of contrast agent (white star). Embolization was performed using a mixture of glubran glue and lipiodol; **D.** Control angiography showed complete exclusion of the lesions

D, cyclophosphamide, vincristine) chemotherapy. She responded well to treatment, and was discharged home in stable, good condition; regular hospitalizations are scheduled to evaluate the course of treatment. The optimal chemotherapy for this kind of choriocarcinoma is not well evidence based due to the rarity of such cases. The recommendation to use methotrexate in low-risk cases and multi-agent therapy (EMA-CO) in high-risk cases is extrapolated from other low- and high-risk gestational diseases and may be an overtreatment in some cases. EMA-CO is the most commonly used combination chemotherapy to treat high-risk gestational trophoblastic neoplasia because it has the best efficacy-to-toxicity ratio.

There are only few case reports of widespread metastasis of choriocarcinoma during pregnancy in the currently available literature and most of them describe patients with intracranial metastases [1–4]. Lemańska et al. [5] reported a case of an urgent embolization of hemorrhagic choriocarcinoma liver metastases in a young female patient. Despite successful occlusion of the culprit vessels and cessation of intraperitoneal bleeding, the patient died two weeks after the procedure. Our case shows that liver metastases of choriocarcinoma should be considered a possibility in pregnant women presenting with hepatic lesions and endovascular embolization as well as prompt termination of pregnancy followed by standard chemotherapy might be safe and effective methods and should be implemented with multidisciplinary involvement.

Article information and declarations

Ethics statement

IRB approved this study – approval number KE-0254/167/06/2023. Patient gave her informed consent for publication.

Author contributions

All authors contributed to the manuscript

Acknowledgments

None.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Romeo DA, Gutman DA, Sirianni J, et al. A Diagnosis of Choriocarcinoma in a Parturient Presenting With Intracranial Hemorrhage. J Med Cases. 2022; 13(4): 151–154, doi: 10.14740/jmc3898, indexed in Pubmed: 35464325.
2. Siwatch S, Suri V, Sikka P, et al. Choriocarcinoma in Ongoing Pregnancy Presenting with Intracranial Metastasis. J Clin Diagn Res. 2016; 10(11): QD01–QD03, doi: 10.7860/JCDR/2016/19344.8769, indexed in Pubmed: 28050451.
3. Mamelak AN, Withers GJ, Wang X. Choriocarcinoma brain metastasis in a patient with viable intrauterine pregnancy. Case report. J Neurosurg. 2002; 97(2): 477–481, doi: 10.3171/jns.2002.97.2.0477, indexed in Pubmed: 12186481.
4. Picone O, Castaigne V, Ede C, et al. Cerebral metastases of a choriocarcinoma during pregnancy. Obstet Gynecol. 2003; 102(6): 1380–1383, doi: 10.1016/s0029-7844(03)00865-2, indexed in Pubmed: 14662230.
5. Lemańska A, Banach P, Stanisławska K, et al. Urgent embolization of hemorrhagic choriocarcinoma liver metastases--case report and review of the literature. Ginekol Pol. 2015; 86(12): 957–961, doi: 10.17772/gp/57871, indexed in Pubmed: 26995948.

VIA MEDICA

CLINICAL VIGNETTE

Ginekologia Polska
2024, vol. 95, no. 6, 506–507

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/gpl.97811

Five consecutive spontaneous pregnancies in a patient after high-dose chemotherapy and peripheral blood stem cell transplantation

Malgorzata Niewiadomska-Kowalczyk[1], Monika Grymowicz[2], Joanna Kacperczyk-Bartnik[1], Ewa Romejko-Wolniewicz[1]

[1]II Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland
[2]Department of Gynecological Endocrinology, Medical University of Warsaw, Poland

INTRODUCTION

The use of high-dose chemotherapy with autologous bone marrow or peripheral blood stem cell transplantation (PBSCT) has increasingly gained acceptance for malignant lymphomas with a high risk of relapse. Ovarian toxicity is a well-recognized potential side effect of the cytotoxic drugs used in most pretransplant conditioning protocols. Spontaneous pregnancies in patients treated with high-dose chemotherapy and autologous stem cell transplants due to malignant lymphomas are extremely rare [1]. We report a case of full reversal of fertility following PBSCT due to aggressive non-Hodgkin's lymphoma.

CASE STUDY

A 25-year-old nulliparous woman was diagnosed with stage IV diffuse large cell lymphoma. The patient underwent high-dose chemotherapy with RCHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and ICE (ifosphamide, cyclophosphamide and etoposide) protocols. Subsequently, the patient was treated with CED (cytoxan, etoposide and dexametasone) to mobilize stem cells. Consolidation of remission was achieved using BEAM (cytarabine, etoposide and melphalan). Peripheral blood stem cell transplantation was performed. The patient presented to our clinic several months after transplantation with amenorrhea, hot flashes, and vaginal dryness. Her follicle-stimulating hormone (FSH) level was 53 IU/L. The patient was placed on estradiol 50 µg/day and dydrogesterone 20 mg for 10 days per month. The patient conceived on replacement therapy about a year and a half after her PBSCT. The pregnancy course was uneventful and at 37 weeks of gestation a healthy baby girl was delivered vaginally. Following delivery, during the breast-feeding period, the patient was placed on oral contraception with desogestrel. Following breast-feeding period, the patient resigned from oral contraception, her menstrual cycles became regular, and the hormonal profile returned to the fertile range. Three months later she spontaneously conceived. The patient became spontaneously pregnant five times. All pregnancies proceeded without complications, and deliveries occurred naturally. Healthy children were born. There was no recurrence of the underlying disease. The patient did not require further oncological treatment.

DISCUSSION

Loss of fertility is a common result of treatment affecting quality of life in cancer survivors. Patient's age, type of cytotoxic agents and their cumulative doses are the most important factors that determine the likelihood of gonadal failure, which might lead to amenorrhoea in many cases resulting in concerns about climacteric symptoms and an increased risk of osteopenia/osteoporosis [2].

Corresponding author:
Malgorzata Niewiadomska-Kowalczyk
II Department of Obstetrics and Gynecology, Medical University of Warsaw, Karowa 2 St., 00–315 Warsaw, Poland
e-mail: mkmnk@o2.pl

Received: 12.10.2023 Accepted: 17.12.2023 Early publication date: 9.02.2024

Chemotherapy with alkylating agents may produce a reduction in primordial follicles, which causes temporary or permanent ovarian function loss. This may manifest as acute ovarian insufficiency during treatment, shortly thereafter or later as premature-early menopause. Five groups of alkylating agents are the first line of chemotherapy. They have the most potent gonadotoxic effect, especially if they are used in combination. Some of such agents are cyclophosphamide, ifosfamide and melphalan, busulfan and chlorambucil, and these are the agents with a higher risk. Cisplatin and carboplatin, with low cumulative doses, and adriamycin, are of intermediate risk. Treatment protocols with bleomycin, actinomycin D, vincristine, methotrexate and fluorouracil, without alkylating agents, are of low risk [3].

Literature is limited to population-based studies comparing pregnancy or birth rates after cancer against unexposed women, or smaller studies using markers of the ovarian reserve as a proxy of infertility among female survivors of cancer [4]. There are no prognostic factors for the return of fertility after stem cell transplantation. Crude birth rate estimated in the biggest study analyzing pregnancy outcome in patients after stem cell transplantation performed in 229 European transplant centers (total number of patients = 37 362) was 0.6% [1]. A retrospective analysis was conducted by Carter regarding the impairment and fertility restoration in 619 women (patients and female partners of male patients who underwent stem cell transplantation) [5]. Pregnancy was reported by 5.5% of patients. 85% of pregnancies ended in live birth. There was no statistically significant increase in the frequency of miscarriages and premature births in these patients compared to general population.

CONCLUSIONS

This is the first report of fertility return after treatment of aggressive non-Hodgkin's disease with high-dose chemotherapy and PBSCT. Although the treatment induced menopause, it was reversed, and the patient conceived five times spontaneously. Patients undergoing conditioned autologous stem cell transplantation should be counseled about the possibility of return of normal ovarian function and pregnancy occurrence after transient menopausal changes.

Article information and declarations

Ethics statement

This manuscriot was prepared in accordance with ethical standards of The Helsinki Declaration.

Author contributions

All authors contributed to preparation of this manuscript. MNK, MG, JKB, ERW participated in patient's management, the literature search, first and final draft preparation.

Funding

None.

Acknowledgments

None.

Conflict of interest

Authors declare no conflicts of interest

REFERENCES

1. Salooja N, Szydlo RM, Socie G, et al. Late Effects Working Party of the European Group for Blood and Marrow Transplantation. Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. Lancet. 2001; 358(9278): 271–276, doi: 10.1016/s0140-6736(01)05482-4, indexed in Pubmed: 11498213.
2. Naessén S, Bergström I, Ljungman P, et al. Long-term follow-up of bone density, general and reproductive health in female survivors after treatment for haematological malignancies. Eur J Haematol. 2014; 93(2): 137–142, doi: 10.1111/ejh.12317, indexed in Pubmed: 24649942.
3. Crnogorac S, Miranovic V. Pregnancy after malignant disease — challenges and possibilities. J Perinat Med. 2018; 46(4): 349–353, doi: 10.1515/jpm-2017-0165, indexed in Pubmed: 29055175.
4. Velez MP, Richardson H, Baxter NN, et al. Risk of infertility in female adolescents and young adults with cancer: a population-based cohort study. Hum Reprod. 2021; 36(7): 1981–1988, doi: 10.1093/humrep/deab036, indexed in Pubmed: 33611573.
5. Carter A, Robison LL, Francisco L, et al. Prevalence of conception and pregnancy outcomes after hematopoietic cell transplantation: report from the Bone Marrow Transplant Survivor Study. Bone Marrow Transplant. 2006; 37(11): 1023–1029, doi: 10.1038/sj.bmt.1705364, indexed in Pubmed: 16604098.

VIA MEDICA

OD PONAD 30 LAT
AKTYWNIE UCZESTNICZYMY W ROZWOJU NAUKI I EDUKACJI MEDYCZNEJ.

- W ciągu roku wydajemy ponad 800 publikacji
- Publikujemy blisko 50 czasopism
- Organizujemy ponad 300 konferencji i webinariów rocznie
- Udostępniamy około 3000 godzin filmów edukacyjnych
- Prowadzimy księgarnię medyczną Ikamed
- Obsługujemy 40 serwisów internetowych, oferujemy aplikacje mobilne

www.viamedica.pl

@ViaMedicaMedicalInformation