Multiple multiparity is a negative prognostic factor for endometrial cancer in Poland

Wielokrotne wielorództwo jest niekorzystnym czynnikiem rokowniczym raka błony śluzowej trzonu macicy w Polsce

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Abstract

Cel pracy: *Background: Nulliparity is one of the most important reproductive risk factors for endometrial cancer. It is still discussed whether multiparity implies a more favorable course of the disease and higher overall survival rates. The aim of the study was to analyze the effect of parity on the overall survival of endometrial cancer patients in Poland.*

Material and method: *A retrospective analysis of parity on survival rates was performed in 810 women treated surgically for endometrial cancer in a single referential center of gynecological oncology.*

Results: *Higher parity was shown to be associated with significantly lower survival rates (p=0.03). Parity turned out to be an independent prognostic factor of survival (HR 1.9). Multiple multiparous women were older at the time of surgery, more often presented with deep myometrial infiltration and with involvement of the cervical stroma and had higher clinical stages of the cancer (only according to FIGO 1988 classification). The group of multiple multiparous women was characterized by significantly lower recurrence rates. Multiple multiparous women significantly more often presented with lower educational level, more often were diagnosed with comorbidities and a history of other malignancies, while breast cancer and colon cancer were of lesser evidence in multiple multiparous endometrial cancer patients.*

Conclusion: *Multiparity turns out to be an unfavorable prognostic factor of survival in Polish women. Unfavorable prognosis in endometrial cancer patients in this group is associated with interactions between risk factors and negative prognostic factors, i.e. the conditions of tumor growth, rather than with the nulliparity itself.*

Key words: **carcinoma** / **endometrioid** / **parity** / **survival analysis** /

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Streszczenie

Nierództwo jest jednym z najważniejszych czynników ryzyka rozwoju raka błony śluzowej trzonu macicy. Wciąż trwają rozważania, czy wielorództwo implikuje bardziej korzystny przebieg choroby i wyższe współczynniki całkowitego przeżycia chorych. Celem pracy jest ocena wpływu rodności na całkowite przeżycie kobiet w Polsce z rakiem błony śluzowej trzonu macicy.

Materiał i metody: *Retrospektywna analiza wpływu rodności na współczynniki przeżycia została przeprowadzona u 810 kobiet leczonych operacyjnie z powodu raka błony śluzowej trzonu macicy w ośrodku referencyjnym ginekologii onkologicznej.*

Wyniki: *Wykazano, że wyższa rodność jest związana z istotnie niższym współczynnikiem całkowitego przeżycia chorych (p=0.03). Rodność okazała się być niezależnym czynnikiem przeżycia chorych (HR 1.9). Wielokrotne wieloródki były starsze w chwili zabiegu operacyjnego, stwierdzano u nich częściej głębokie naciekanie mięśniówki macicy i częściej naciek podścieliska szyjki macicy oraz wyższe stopnie zaawansowania nowotworu (wyłącznie w klasyfikacji FIGO z 1988 roku). Grupa wielokrotnych wieloródek charakteryzowała się znacząco niższym współczynnikiem nawrotów choroby. Kobiety te statystycznie częściej cechowało posiadanie niższego wykształcenia, częściej również stwierdzano u nich obecność chorób towarzyszących w tym również występowanie innych nowotworów złośliwych. W grupie tej jednakże rzadziej występowały nowotwór piersi i jelita grubego niż u pozostałych kobiet.*

Wnioski: *Wielorództwo okazuje się być niekorzystnym czynnikiem prognostycznym przeżycia u Polek. Niekorzystne rokowanie w raku błony śluzowej trzonu macicy w tej grupie jest mniej związane z nierództwem a zdecydowanie bardziej związane z interakcją niekorzystnych czynników ryzyka i negatywnych czynników prognostycznych, które tworzą sprzyjające okoliczności i środowisko dla wzrostu nowotworu.*

Słowa kluczowe: **endometrial cancer** / **secondary neoplasm** / **molecular analysis** /

Introduction

Endometrial cancer is the most frequent female genital malignancy in the developed European and North American countries, with the incidence rates up to 12.8 and 16.4 per 100 000, respectively [1, 2]. Noticeably, despite only a moderate increase in the incidence of endometrial cancer, the mortality of this malignancy has doubled since 1987 [2, 3]. In Poland, however, the increasing mortality of endometrial cancer was associated with a dramatic increase in the incidence of this malignancy. No earlier than 10-15 years ago, endometrial cancer emerged as the most frequent female genital malignancy in Poland (overtaking cervical cancer) and its incidence rate reached 15.1 per 100 000 in 2012 [4].

Such dramatic increase in the incidence of endometrial cancer in Poland was likely associated with changes in demographic, economic and health structure of Polish women, resulting from an intensive development of the country after the political transformation of 1989. This was inter alia reflected by accumulation of factors that promote cancer development, such as population aging, improved material status, higher prevalence of obesity, hypertension and diabetes mellitus, and growing incidence of other malignancies (e.g. breast cancer and colorectal cancer).

Nulliparity is one of the most important reproductive risk factors for endometrial cancer. Due to physiological increase in progesterone concentration, pregnancy is postulated to protect against endometrial cancer development, especially in view of the unbalanced estrogens hypothesis. The protective effect of progesterone is observed not only during a pregnancy but also many years thereafter, and is further potentiated by each subsequent gestation. According to Albrektsen et al. [5] and other authors [6-9], the protective effect of progesterone can be also observed in the case of already present endometrial cancer. Therefore, multiple multiparous women were shown to be characterized by a more favorable course of the disease and higher overall survival rates.

The aim of this study was to analyze the effect of parity on the overall survival of endometrial cancer patients.

Material and methods

The study included a total of 810 women treated surgically at the Department of Gynecology, Medical University of Gdansk, between 1985 and 2009. Originally, a group of 1 406 patients treated surgically for uterine cancer or endometrial hyperplasia were enrolled. However, the individuals who were eventually diagnosed with carcinosarcoma (n=39) or metastatic uterine cancer of a non-uterine origin (n=45) were excluded from the analysis, as well as the patients in whom endometrial hyperplasia was not identified as endometrial cancer on histopathological analysis (n=248), women subjected to neoadjuvant radiotherapy (n=19) and cases with incomplete follow-up documentation (n=245).

Therefore, a total of 810 women (57.6% of the originally enrolled group) were eventually analyzed, including:

1) 754 (93.1%) patients in whom endometrial cancer was found both by primary pathological examination of endometrial biopsy specimens (obtained during curettage or hysteroscopy) and by the final examination of surgical specimen from hysterectomy;
2) 34 (4.2%) patients qualified to surgery due to endometrial

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hyperplasia and eventually diagnosed with endometrial cancer based on the final examination of surgical specimen from hysterectomy; and

3) 22 (2.7%) patients in whom endometrial cancer was found on primary pathological examination of endometrial biopsy specimens (obtained during curettage or hysteroscopy) and removed completely during the endometrial abrasion.

The type and extent of surgery were determined on the basis of general health status of each patient, comorbidity profile and the result of intraoperative staging. The patients were followed-up at the Department's Outpatient Clinic according to a standard protocol. Only the data of women who completed at least 5-year follow-up period until February 2013 were analyzed.

Statistical analysis of the results was carried out with STATISTICA 5.0 PL. package. The Pearson's chi-square test, Yates' chi-square test and Mann-Whitney U-test were used for intergroup comparisons. The survival rates of endometrial cancer patients were determined according to the Kaplan-Meier method and compared between the groups with an aid of the log-rank and Cox F tests. The intergroup differences were considered significant at $p < 0.05$.

The protocol of the study was submitted to the Local Bioethics Committee (Independent Bioethics Commission for Research, Medical University of Gdansk, Poland), and in line with respective Polish legislation was granted a waiver from the ethics approval.

Results

87.9% (n=710) of the endometrial cancer women were multiparous, and the remaining 12.1 % (n=98) were nulliparous. 16.7% (n=135) of the multiparous patients had a history of one delivery; the remaining ones delivered twice (34.9%, n=282), three (17.8%, n=144), four (10.3%, n=83) and five or more times (10,5%, n=8.2).

Higher parity was shown to be associated with significantly lower survival rates (p=0.03; Figure 1). Parity turned out to be an independent prognostic factor of survival (HR 1.9).

Nulliparous patients and multiparous women with endometrial cancer did not differ significantly in terms of their overall survival rates (p=0.48). Moreover, no significant differences were found when the overall survival rates of nulliparous patients were compared with those of women having a history of 1-3 deliveries (p=0.7). However, at least four deliveries were identified as a factor exerting significant unfavorable effect on the overall survival rates (p=0.0007), implying that multiple multiparas may have worse prognosis than multiparous women characterized by lower parity (p=0.0006). Nevertheless, we did not find a significant difference between the survival rates of nulliparous and multiple multiparous women (p=0.09).

Further analysis revealed (Table I) that multiple multiparous women were 3.8 years older at the time of surgery (p<0.00001), and significantly more often that the remaining patients presented with deep (≥50%) myometrial infiltration (p=0.0008) and involvement of the cervical stroma (p=0.01). The two groups of patients did not differ in terms of the frequency of lymph node involvement (p=0.5), parametrial infiltration (p=0.5), infiltration of the lymphovascular space (p=0.7) and presence of cancer cells in peritoneal lavage fluid (p=0.2). Nevertheless, multiple multiparous women significantly more often presented with higher clinical stages of endometrial cancer according to the 1988 FIGO classification (p=0.005). However, this intergroup difference was no longer significant if the 2009 FIGO classification was used. Nonetheless, multiple multiparous women were diagnosed with the stage II of this classification twice as frequently as the remaining patients (p=0.01). The group of multiple multiparous women was characterized by similar recurrence rates (p=0.8). Socioeconomic analysis revealed that multiple multiparous women significantly more often presented with lower educational level (p<0.0001). Furthermore, they significantly more often were diagnosed with obesity (p<0.0001), hypertension (p=0.006) or diabetes mellitus (p=0.005), yet equally frequent had a history of other malignancies (p=0.2). While breast cancer and colon cancer (33.3% and 25.3%, respectively) were most frequent malignancies found in nulliparous patients and multiparous women with low parity, they were of lesser evidence in multiple multiparous endometrial cancer patients (23.8% and 19.0%, respectively).

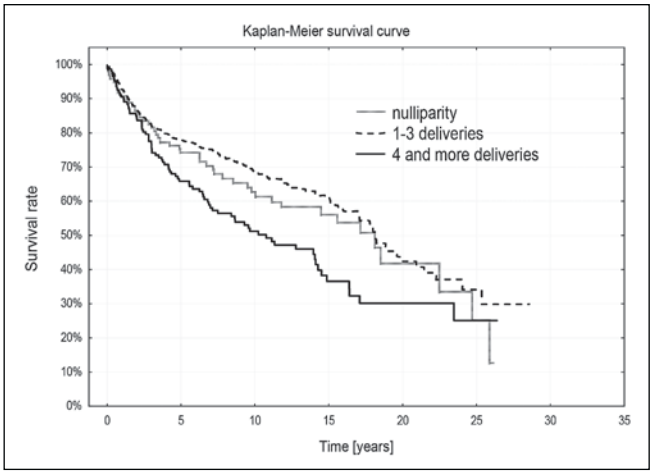

Figure 1. Survival rates of endometrial cancer patients: A. nulliparous women, B. multiparous women with low parity (one to three deliveries), C. multiple multiparous women (at least four deliveries) (p=0.0006, chi-square test).

Discussion

Multiparity is an established factor protecting against endometrial cancer development [5, 6, 9-16]. Many previous studies [6-9] showed that multiparous women are characterized by less aggressive phenotype of endometrial cancer and higher overall survival rates than nulliparas. This phenomenon can be explained by two mechanisms. First, the protective effect may be associated with high concentrations of progesterone and relatively lower concentrations of estrogens observed during pregnancy; second, it may result from the exfoliation of precancerous endometrial cells during the third phase of labor [10, 11, 12]. Noticeably, we did not confirm the protective effect of multiparity on women in our study. Not only did we not find a significant difference between the overall survival rates of nulliparous and multiparous women, but also showed that higher parity was associated with lower survival rates. Furthermore, higher number of labors turned out to be an independent negative prognostic

Table I. Comparison of multiple multiparous women (parity ≥4) and women of low parity or nulliparous (parity <4).

Feature		Parity < 4		Parity ≥4		*P value*
age of patients	*mean (±SD*)*	61.7 (±9.7)		65.5 (±8.2)		<0.00001
	range	26.4 – 88.8		47.4 – 88.5		
		n	*%*	*n*	*%*	
FIGO stage 2009	1	537	81.5	118	79.2	0.07
	2	34	5.2	16	10.7	
	3	58	8.8	10	6.7	
	4	30	4.6	5	3.4	
FIGO stage 1988	1	487	73.9	96	64.4	0.005
	2	77	11.7	34	22.8	
	3	65	9.9	14	9.4	
	4	30	4.6	5	3.4	
Bokhmann's type of endometrial cancer	I	497	76.9	112	76.2	0.9
	II	149	23.1	35	23.8	
grading	G1	305	62.6	61	55.0	0.21
	G2	155	31.8	40	36.0	
	G3	27	5.5	10	9.0	
myometrial invasion	<50%	353	54.2	58	38.9	0.0008
	≥50%	298	45.8	91	61.1	
cervical stromal invasion		66	10.5	26	18.3	0.01
parametrial infiltration		10	2.3	3	3.7	0.5
infiltration of the lymphovascular space		19	4.4	3	3.7	0.7
cancer cells in peritoneal lavage fluid		15	4.9	6	9.2	0.2
lymph node metastasis		26	14.2	3	9.4	0.5
recurrence		40	17.8	6	19.4	0.8
education	university or general secondary	131	76.7	5	20.0	<0.0001
	vocational or primary	40	23.4	20	80.0	

**SD- standard deviation*

factor in endometrial cancer patients. Further analysis revealed that multiparous women were older at the time of surgery and more often presented with higher clinical stages of endometrial cancer, deep myometrial invasion and involvement of the cervical stroma.

Albrektsen et al. [5] proved that nulliparous women with endometrial cancer have poorer prognosis than multiparas; the nulliparas participating in this study were older and presented with higher clinical stages of the malignancy. Similar relationship was also indicated by Salvesen et al. [9]; moreover, they showed that nulliparous women presented with higher grade endometrial cancers. The recently published findings of Schonfeld et al. [17] do not support the hypothesis that nulliparous women are at higher risk of endometrial cancer due to greater hormonal exposure. In turn, Hachisug et al. [18] showed that nulliparity is associated with worse survival only in the case of older women with high-stage endometrial cancers.

Apart from unfavorable characteristics of endometrial cancer, multiparous women participating in our study were exposed to additional negative prognostic factors, such as concomitant obesity and systemic conditions included in the metabolic syndrome, such as arterial hypertension and diabetes mellitus. Moreover, compared to other women, multiple multiparas significantly more often had a history of other malignancies, but these were rarer neoplasms that usually co-exist with endometrial cancer, i.e. breast and colorectal cancers.

The contrary relationship between parity and overall survival rates of our participants likely reflected sociodemographic situation in Poland. Until recently, multiparity was considered an indicator of worse socioeconomic status of Polish women, which is partially consistent with our findings of lower education and worse occupational status of the multiparas. According to EUROSTAT, there is an inverse relationship between fertility rates and national wealth, and women from developing countries still have more children than their counterparts from the developed economies. Taking the abovementioned observations into account, one should note that the period when our endometrial cancer patients have had children corresponded to a time when Poland was considered a developing country.

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For more than ten years, the global demographic trends of developed world had reversed. However, the demographic situation of Poland and other Central and Eastern European countries (Czech Republic, Slovakia, Hungary, Lithuania), expressed by such measures as fertility, Total Fertility Rate (TFR; mean number of children that would be born alive to a woman during her lifetime if she were to pass through her childbearing years conforming to the age-specific fertility rates of a given year), mean age of women at childbirth, and fertility to economic status ratio, still resembles that observed about 10-20 years earlier in the rest of well-developed European states. The fertility rates of women from the Central and Eastern Europe constantly decrease, from 2.1-2.2 in 1980 to 1.2-1.3 in 2011. Also TFR follows similar pattern, and mean age at childbirth is still below 30 years. In turn, after a transient decrease in fertility, to 1.45 in 2001, a slight increase in this parameter, up to 1.56 in 2012, is observed in well-developed European countries [19]. This phenomenon was probably associated with a trend to postpone childbirth over the age of 30 years. Older age at childbirth may likely explain different effects of childbearing on the outcome of endometrial cancer observed in women from developed European countries. Albrektsen et al. [5] showed that maternal status influences prognosis in endometrial cancer patients; however, it is the time elapsed from the last childbirth which is crucial for the prognosis. The shorter the time, the better the prognosis. Although we did not analyze this parameter in our study, data from literature suggests that Polish multiple multiparous women give birth to either their first or their last child at younger age than their counterparts from well-developed countries (e.g. France, Denmark, Finland and the Netherlands), and contrary to the latter, usually have no more than one or two children [20, 21].

Conclusions

Our findings suggest that fertility is not an solitary negative prognostic factor in endometrial cancer patients. The abovementioned results suggest that unfavorable prognosis in endometrial cancer patients is associated with interactions between risk factors and negative prognostic factors, i.e. the conditions of tumor growth, rather than with the nulliparity itself.

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References

1. Jemal A, Bray F, Center MM, [et al.]. Global cancer statistics. *CA Cancer J Clin.* 2011, 61, 69-90.
2. GLOBCAN 2008. Estimated cancer Incidence, Mortality, Prevalence and Disability-adjusted life years (DALYs) Worldwide in 2008. International Agency for Research on Caner. World Health Organization. Available from: URL:http://globocan.iarc.fr/
3. Silverberg E, Lubera J. Cancer statistics, 1987. *CA Cancer J Clin.* 1987, 37, (1), 2-19.
4. Polish National Cancer Registry. Department of Epidemiology and Cancer Prevention. Available from: URL:http://onkologia.org.pl/raporty/#tabela_nowotwor
5. Albrektsen G, Heuch I, Wik E, [et al.]. Parity and time interval since childbirth influence survival in endometrial cancer patients. Int J Gynecol Cancer. 2009, 19, (4), 665-669.
6. Løchen ML, Lund E. Childbearing and mortality from cancer of the corpus uteri. *Acta Obstet Gynecol Scand.* 1997, 76, (4), 373–377.
7. Hachisuga T, Fukuda K, Hirakawa T, [et al.]. The effect of nulliparity on survival in endometrial cancer at different ages. *Gynecol Oncol.* 2001, 82, (1), 122-126.
8. Salvesen HB, Akslen LA, Albrektsen G, [et al.]. Poorer survival of nulliparous women with endometrial carcinoma. *Cancer.* 1998, 82, (7), 1328-1333.
9. Salvesen HB, Akslen LA, Albrektsen G, [et al.]. Is the risk of cancer of the corpus uteri reduced by a recent pregnancy? A prospective study of 765,756 Norwegian women. *Int J Cancer.* 1995, 61, (7), 485-490.
10. Franceschi S. Reproductive factors and cancers of the breast, ovary and endometrium. *Eur J Cancer Clin Oncol.* 1989, 25, (12), 1933-1943.
11. Kvale G, Heuch I, Ursin G. Reproductive factors and risk of cancer of the uterine corpus: a prospective study. *Cancer Res.* 1988, 48, (21), 6217-6221.
12. Pfeiffer RM, Mitani A, Landgren O, [et al.]. Timing of births and endometrial cancer risk in Swedish women. *Cancer Causes Control.* 2009, 20, (8), 1441-1449.
13. Dossus L, Allen N, Kaaks R, [et al.]. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer.* 2010, 127, (2), 442-451.
14. De Ward F, De Ridder CM, Baanders-van Halewyn EA, [et al.]. Endometrial cancer in a cohort screened for breast cancer. *Eur J Cancer Prev.* 1996, 6, (2), 99–104.
15. Chan TF, Wu CH, Changchien CC, [et al.]. Mortality from breast, endometrial and ovarian cancers among grand multiparous women in Taiwan. *Aust N Z J Obstet Gynaecol.* 2011, 51, (6), 548-552.
16. Salvesen HB, Akslen LA, Albrektsen G, [et al.]. Poorer survival of nulliparous women with endometrial carcinoma. *Cancer.* 1998, 82, (7), 1328-1333.
17. Schonfeld SJ, Hartge P, Pfeiffer RM, [et al.]. An aggregated analysis of hormonal factors and endometrial cancer risk by parity. *Cancer.* 2013, 119, (7), 1393-1401.
18. Hachisuga T, Fukuda K, Hirakawa T, [et al.]. The effect of nulliparity on survival in endometrial cancer at different ages. *Gynecol Oncol.* 2001, 82, (1), 122-126.
19. EUROSTAT Total fertility rate – online report. Available from: URL:http://ec.europa.eu/eurostat/tgm/refreshTableAction.do?tab=table&plugin=1&pcode=tsdde220&language=en
22. Polish Yearbook 2011 (ed.) Domochowska H. Zakład Wydawnictw Statystycznych. 2012, 181-209.
21. Brainerd E. Can government policies reverse undesirable declines in fertility? Available from: URL:http://wol.iza.org/articles/can-government-policies-reverse-undesirable-declines-infertility