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Pregnancy beyond the age of 40 – the influence of parity on perinatal outcome

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Abstract

OBJECTIVE: The aim of the study was to compare the pregnancy course and neonatal outcome in women at least 40 years old during conception.

DESIGN: Data were collected on the basis of medical records of patients who gave birth between 2009–2014 at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw. Women enrolled were at least 40 years old at the moment of conception and delivered after 22 completed weeks of gestation – they were also assigned into 2 groups: primiparas and multiparas. Demographic features, pregnancy and delivery complications, mode of delivery and neonatal outcome were analyzed and compared.

RESULTS: 9760 women delivered at the Department during the study period, among them 193 met the inclusion criteria for the study: 40 primiparas (average age 40.9±1.14) and 153 multiparas (average age 41.3±1.35).

No relation between parity and preterm delivery was observed (5% primiparas vs 11.1% multiparas; $p>0.05$). However, gestational age at delivery was associated with the number of pregnancies – the higher the pregnancy number, the lower the gestational age ($p=0.009$; R=–0.188). Primiparity was associated with an increased rate of oligohydramnios (RR=4.78; 95%CI 1.15–20.63) and pregnancy induced hypertension (RR=2.34; 95%CI 0.93–5.58).

Primiparas had a significantly greater risk of operative delivery (RR=1.83; 95%CI 1.42–2.12) and unsuccessful labor inductions (RR=3.60; 95%CI 1.04–5.29). They were more often diagnosed with fibroids (RR=3.04; 95%CI 1.15–7.81). No relations between parity and birth weight, fetal abnormalities or Apgar score were observed.

CONCLUSIONS: Delayed childbearing of a first child seems to increase the risk of perinatal complications, which is important for counseling purposes.

ORIGINAL ARTICLE

INTRODUCTION

Over the last two decades there has been a remarkable shift in the demographics of child-bearing. The birthrate has decreased in many developed countries – women conceive when they are older and they decide to give birth to fewer children. The changes in the family pattern, life and career expectations, as well as greater access to contraception are some of the factors leading to delayed motherhood (Millis & Lavender 2011; Kenny *et al.* 2013; Carolan 2003). On the other hand, an enormous progress in infertility treatment observed over the last 30 years and widespread access to assisted reproductive technologies, including in vitro fertilization and oocyte donation, enabled many women – also those over the age of 40 – to become mothers (Millis & Lavender 2011; Yogev *et al.* 2010). Therefore, pregnant women beyond the age of 40 might either experience their first delivery due to the history of infertility or postponed decision, or subsequent delivery that may be planned or associated with inappropriate use of contraceptive methods.

The risk of adverse obstetric and perinatal outcomes increases continuously with maternal age. The relationship between maternal age and incidence of perinatal complications is reflected with a J-shaped curve – a significant increase in the incidence is observed after the age of 35 and a steep rise after the age of 40 (Millis & Lavender 2011; Koo *et al.* 2012). Therefore, the age of 40 is considered as an optimal cutoff point in terms of identifying high-risk pregnancies (Chan & Lao 1999). It is well known that advanced maternal age may be associated with a higher risk of complications. There are however insufficient data concerning the influence of parity in women of advanced age on the obstetric outcome (Koo *et al.* 2012; Chan & Lao 2008; Lisonkova *et al.* 2010). The aim of this study was to compare the course of pregnancy and delivery, as well as neonatal outcome in primiparous and multiparous women beyond the age of 40 and to investigate whether parity is an additional risk factor in such pregnancies.

MATERIAL AND METHODS

The study is a retrospective analysis of the medical records of patients who delivered at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, between January 2009 and December 2014. Women enrolled in the study were at least 40 years old at conception and were in singleton pregnancies. Eligibility for the study was limited to pregnancies of at least 22 weeks of gestation (basing on the last menstrual period and verified by the first trimester ultrasound). A total of 193 women beyond the age of 40 fulfilled the inclusion criteria and depending on the obstetrical history they were assigned to the group of primiparas or multiparas. Collected data were compared with respect to parity.

Analyzed variables included demographic information, pre-existing maternal medical conditions, obstetric outcome (pregnancy complications and delivery mode), intrapartum and perinatal complications.

The demographic features included maternal age, body mass index (BMI), gravidity, parity, history of spontaneous abortion, history of infertility, *in vitro* fertilization (IVF) use in current pregnancy. Pre-existing maternal medical conditions included chronic hypertension, pre-gestational diabetes, thyroid diseases and fibroids. Pregnancy complications consisted of: gestational hypertension (≥140/90 mmHg measured on two separate occasions >20 weeks of gestation), gestational diabetes mellitus (GDM – diagnosed basing on oral glucose tolerance test), preeclampsia (defined as gestational hypertension with proteinuria of >300 mg in daily urine sample), oligohydramnios (AFI: amniotic fluid index <5 percentile on ultrasound), polihydramnios (AFI>90 percentile), intrauterine growth restriction (IUGR – estimated fetal weight <10 percentile on ultrasound), fetal macrosomia (>90 percentile), placenta praevia, preterm premature rupture of membranes (PPROM – PROM prior to completed 37 weeks of gestation). Mode of delivery was classified as vaginal delivery, instrumental delivery or cesarean section (CS). Indications for cesarean section were either elective or emergency, subdivided into categories including history of infertility, previous CS, fibroids, labor induction failure and fetal distress. Intrapartum complications included postpartum hemorrhage and perineal lacerations. Perinatal outcome consisted of mean gestational age, preterm delivery, very preterm delivery, extremely preterm delivery, mean birth weight, low birth weight, very low birth weight extremely low birth weight, 1-minute and 5-minute Apgar score and fetal abnormalities.

The policy of the department regarding vaginal birth after cesarean section (VBAC) is to offer vaginal delivery to patients after one previous CS for a non-recurrent cause, provided there are no major obstetric indications for cesarean section and the patient signs an informed consent for VBAC.

Delivery prior to 37, 32 or 28 completed weeks of gestation was considered as preterm birth, very preterm birth and extremely preterm birth, respectively. Birth weight below 2 500, 1 500 and 1 000 g was considered as low birth weight (LBW), very low birth weight (VLBW) and extremely low birth weight (ELBW), respectively.

Patients' characteristics were presented as numbers of cases and percentages for categorical data, and as means with standard deviations (SD) for continuous data. The groups were compared by chi-squared test and exact Fisher's test for categorical variables. For non-parametric statistics U-Mann Whitney test was used. Statistical analysis was performed with the use of Statistica 12.0 software, with p-value <0.05 considered significant. Relative Risks (RR) and 95% confidence intervals (CI) were calculated. All p-values were two-tailed.

RESULTS

Out of the 9760 pregnancies delivered at the Department over the study period, 193 (1.97%) met the inclusion criteria. 40 (20.7%) of the patients were primiparous and 153 (79.3%) multiparous. The age distribution with respect to parity is shown in Table 1.

Maternal characteristics are presented in Table 2. There was no difference in BMI at conception (23.63 vs 24.54) or weight gain during pregnancy (12.48 vs. 14.19) between the primiparous and multiparous mothers. There were, however, significantly more women with a history of infertility in the primiparous group (40% vs. 12.4%, $p<0.001$) and more patients in this group conceived using IVF (32.5% vs. 3.3%, $p<0.001$) (Table 2). The number of patients with fibroids was also significantly higher in the primiparous group (20% vs. 6.5%, $p=0.028$, OR=3.04; 95%CI 1.15–7.81).

Primiparity was associated with an increased rate of oligohydramnios (12.5% vs. 2.61%, $p=0.008$; RR=4.78 95%CI 1.15–20.63) and gestational hypertension (20% vs. 8.56%, $p=0.039$, RR=2.34, 95%CI 0.93–5.58%). There were no statistically significant differences between primiparas and multiparas with regard to other analyzed complications. The results of the analysis are presented in Table 3.

The analysis of the delivery in the study group is presented in Table 4. Primiparas had a significantly greater risk of cesarean delivery (85% vs. 46.4%, $p<0.001$ RR=1.83; 95%CI 1.42–2.12) and failed labor inductions (80% vs. 22.2%, $p=0.02$; RR=3.60 95%CI 1.04–5.29). The groups differed with regard to the indications for cesarean sections – the main indication in primiparas was the history of infertility (17.6%), while in multiparas delivery after previous CS (49.3%). Fibroids were also a common indication for cesarean section in primiparas (8.8% vs. 1.6%, $p=0.096$). Other indications included fetal distress, risk of intrauterine infection and fetal malpresentation. The analysis of the study group proved a decrease in blood loss during labor with the higher number of pregnancy in multiparas ($p=0.005$, R=–0.206).

There was no relation between parity and preterm delivery in the studied material. The rate of preterm deliveries was 5% in primiparas and 11.1% in multiparas ($p=0.25$), while mean gestational age was 38.6±1.3 and 38.0±2.3, respectively. A weak negative correlation was observed in multiparas between the number of pregnancy and gestational age at delivery ($p=0.009$, R=–0.188).

There were no differences in the neonatal outcome with regard to parity – results of the analysis are presented in Table 5.

Tab. 1. The distribution of age and parity in the study group.

Age [yrs]	Primiparas (n=40)	Multiparas (n=153)
40	17	52
41	15	45
42	5	22
43	1	24
44	1	6
45	1	3
46	0	1

Tab. 2. Maternal demographic features and pre-existing medical conditions.

	Primiparas (n=40)	Multiparas (n=153)	*p*-value
Mean maternal age*	40.93±1.14	41.35±1.35	0.09
Mean BMI*	23.63	24.54	0.15
Mean weight gain	12.48	14.19	0.40
Gravidity**	1.00	3.00	<0.001
Parity**		2.00	–
History of spontaneous abortion (%)	17 (42.5)	59 (38.6)	0.65
Number of spontaneous abortions (history)	0.68±1.05	0.54±0.87	0.65
History of infertility (%)	16 (40)	19 (12.4)	<0.001
Use of IVF in current pregnancy (%)	13 (32.5)	5 (3.3)	< 0.001
Pre-pregnancy hypertension (%)	0	12 (7.8)	0.067
Hyperthyroidism (%)	0	5 (3.3)	0.25
Hypothyroidism (%)	5 (12.5)	25 (16.4)	0.55
Pre-pregnancy diabetes mellitus (%)	1 (2.5)	3 (2.0)	0.83

* At conception
** Median

Tab. 3. The analysis of pregnancy complications in primiparas and multiparas.

	Primiparas (n=40)	Multiparas (n=153)	RR	95% CI	*p*-value
Gestational hypertension (%)	8 (20)	13 (8.6)	2.34	0.93–5.58	0.039
Preeclampsia (%)	2 (5.1)	4 (2.6)	1.95	0.25–11.97	0.43
GDM (%)	8 (20)	31 (20.3)			0.93
Oligohydramnios (%)	5 (12.5)	4 (2.6)	4.78	1.15– 20.63	0.008
Polihydramnios (%)	0 (0)	2 (1.3)			0.47
IUGR (%)	2 (5)	5 (3.3)			0.60
Fetal macrosomia (%)	3 (7.5)	7 (4.6)			0.46
Placenta praevia (%)	0 (0)	4 (2.6)			0.30
PPROM (%)	0 (0)	4 (2.6)			0.30

Tab. 4. The mode of delivery and delivery complications in primiparas and multiparas.

	Primiparas (n=40)	Multiparas (n=153)	RR	95% CI	*p*-value
Vaginal delivery (%)	6 (15)	79 (51.6)	0.29	0.12–0.61	<0.001
Instrumental delivery (%)	0	3 (2)			0.37
Cesarean section (%)	34 (85)	71 (46.4)	1.83	1.42–2.12	<0.001
Labor induction (%)	5 (12.5)	27 (17.6)			0.43
Failed labor induction (%)	4 (80)	6 (22.2)	3.60	1.04–5.29	0.02
Elective CS (%)	18 (54.5)	52 (73.2)	0.75	0.50–1.04	0.07
Emergency CS (%)	15 (45.5)	19 (26.8)	1.70	0.92–2.98	0.07
Postpartum hemorrhage (%)	0	9 (5.9)			0.12
Perineal lacerations	1 (2.5)	13 (8.5)			0.19

DISCUSSION

Both in high and low income countries a trend to delay childbearing has been observed, especially among women who are better educated and have financial stability (Chan & Lao 2008). As a result of demographic changes, advanced maternal age is nowadays considered to be beyond 40 years of age instead of 35, as earlier (Callaway *et al.* 2005). Nevertheless, women who delay child-bearing are at increased risk of infertility, as it is naturally more difficult to conceive (Johnson & Tough 2012). The problem of fertility in advancing age is a result of rapidly decreasing number of ovarian follicles and their lower sensitivity to gonadotrophins (Gadomska *et al.* 2010). However, the leading cause of fertility problems is poor oocyte quality. A high rate of mothers with a history of infertility was identified in the studied material in the group of primiparas. Every third of them was pregnant by means of IVF. Therefore it might be suspected that the most important reason for delayed child-bearing in this group of patients was failure to conceive and not a conscious decision.

The rate of deliveries in women over 40 years of age varies from 1.9% in older studies (Jolly *et al.* 2000) to 3.13–3.9% in more recent ones (Hoffman *et al.* 2007; Chan & Lao 2008; Kenny *et al.* 2013). In our study the rate was comparable to older reports and equaled 1.97% (however, few cases of multiple pregnancies were excluded). The rate of primiparas among mothers over 40 also varies from 14% (Jahromi & Husseini 2008) to as many as 33% (Chan & Lao 2008), however, the majority of authors reported rates around 20–25%, which is similar to our results (20.7%) (Kenny *et al.* 2013; Jolly *et al.* 2000).

Delayed child-bearing is associated with an increased risk of obstetrical and perinatal complications, among them gestational hypertension and preeclampsia, gestational diabetes and preterm delivery. Care providers need to be aware of that fact in order to optimize management to ensure the best possible outcome (Johnson & Tough 2012; Lie *et al.* 1998; Callaway *et al.* 2005). In more recently published studies the rates of perinatal mortality and morbidity in older women are obviously higher (Reddy *et al.* 2006; Josephs *et al.* 2005; Jacobsson *et al.* 2004). Additionally, parity is definitely a less studied, but an important confounding factor for adverse obstetric outcome (Chan & Lao 2008).

Gestational hypertension (GH) and preeclampsia (PE) are generally more often diagnosed in mothers of advanced age – their incidence varies from 3.2% to

Tab. 5. Neonatal outcome in primiparas and multiparas.

		Primiparas (n=40)	Multiparas (n=153)	*p*-value
Mean birth weight [g]		3325.7	3250.5	0.77
Fetal abnormalities (%)*		3 (7.5)*	4 (2.6)*	0.14
Preterm birth (%)		2 (5.0)	17 (11.1)	0.25
Very preterm birth (%)		0	1 (0.7)	0.61
Extremely preterm birth (%)		0	3 (2.0)	0.37
Low birth weight (%)		3 (7.5)	13 (8.5)	0.84
Very low birth weight (%)		0	3 (2.0)	0.37
Extremely low birth weight (%)		0	2 (1.3)	0.47
1 minute Apgar score	8–10	87.5%	92.8%	0.28
	4–7	12.5%	5.2%	0.10
	0–3	0%	2%	0.37
5 minute Apgar score	8–10	100%	98%	0.37
	4–7	0%	0%	1.00
	0–3	0%	2%	0.37

*Fetal abnormalities included:
– Primiparas: Klinefelter syndrome, mosaic Turner syndrome, set of anomalies (VACTERL suspected)
– Multiparas: 47XXX aneuploidy, trisomy 13, Dandy-Walker syndrome and fetal pyelectasis
The neonates with 47XXX and trisomy 13 died shortly after birth. The mother of the neonate with Dandy-Walker syndrome developed HELLP syndrome.

18% for GH and 2.4–10.7% for PE (Yogev *et al.* 2010; Jolly *et al.* 2000; Jahromi & Husseini 2008; Diejomaoh *et al.* 2006). Additionally, the higher incidence of GH in primiparas of advanced maternal age is a well-known fact (Chan & Lao 1999). The risk of developing that particular complication in our material was also more than 2 times greater than in multiparous mothers – it reached 20%. It is moreover important to notice that a very high rate of oligohydramnios was detected in the primiparas in our study group (12.5%). Oligohydramnios is reported in 1–8% of pregnancies in Poland. The big span might be due to various criteria for oligohydramnios (AFI <10 percentile for gestational age, largest vertical amniotic fluid pocket less than 2 cm). Only few researchers reported data regarding oligohydramnios in older mothers – the rate was also higher than in younger population and reached 9% in women older than 44 years (Yogev *et al.* 2010).

Gestational diabetes is another more frequently diagnosed complication in women of advanced age. Jolly *et al.* estimated that the risk for older mothers is almost 4 times higher (Jolly *et al.* 2000). Various authors reported rates around 8–10% in women over 40 years of age with no data regarding parity (Yogev *et al.* 2010; Ludford *et al.* 2012; Hoffman *et al.* 2007). Chan and Lao reported a very high rate of GDM: 24.9% in primiparas and 31% in multiparas over 40 (Chan & Lao 2008). Regardless of parity, the rate of GDM in the study group (20%) was very high in comparison to the general incidence in Poland reported to be around 3–5% (Polish Gynecological Society 2011). This might be due to the fact that the Department is a tertiary center with an outpatient clinic for gestational diabetes, not only due to the advanced age of the mothers.

Preterm delivery is by far one of the most important perinatal outcomes. The majority of papers reported that the risk of delivering preterm is greater in advanced age mothers, with significant relative risks of 1.1–1.5 and rates ranging from 5.5% to 12.8% (Yogev *et al.* 2010; Ludford *et al.* 2012; Hoffman *et al.* 2007; Chan & Lao 2008; Kenny *et al.* 2013). Although the differences in the rate of preterm deliveries between studied subgroups in our material seemed important from the clinical point of view, it was not statistically significant (5% in primiparas and 11.1% in multiparas). It is probably due to the small number of analyzed subgroups. The general incidence of preterm delivery in Poland is reported to be around 6.9% (Polish Gynecological Society 2012). Chan and Lao also did not observe any significant elevation in neither of the groups, however, there were more preterm deliveries in primiparas in their study (Chan & Lao 1999).

The most significant difference between the subgroups of patients was observed in the incidence of cesarean deliveries. Chan and Lao reported similar results with respect to parity, but the CS rate presented in their study was significantly lower (49%) (Chan & Lao 1999). The reasons contributing to such high rates

of CS in both primiparas (85%) and multiparas (46.4%) are complex. First of all, the number of cesarean sections performed worldwide is constantly increasing (Micek *et al.* 2014). Moreover, the increased risk for CS might be caused by the deterioration of uterine activity occurring with advancing age reported by some authors (Jolly *et al.* 2000). Higher incidence of diabetes mellitus and hypertension with its complications are also factors contributing to operative deliveries (Jahromi & Husseini 2008). Above all, due to high rate of infertility treatment and IVF pregnancies, especially in the primiparous group, obstetricians and patients themselves are less likely to take risks associated with prolonged delivery. A decrease in the "decision threshold" for cesarean sections in such patients is referred to as "precious baby syndrome" (Carolan *et al.* 2003; Diejomaoh *et al.* 2006; Koo *et al.* 2012). Psychological exhaustion of patients over 40 may also play a role in this high rate of operative interventions (Gadomska *et al.* 2010).

The parity of advanced age mothers had no influence on neonatal outcome in the studied material. The incidence of LBW, VLBW and ELBW was quite low. This supports previous findings suggesting that the mean birth weight might not be affected by maternal age (Chan & Lao 1999; Jahromi & Husseini 2008; Ates *et al.* 2013).

Good general condition of newborns in 5th minute according to Apgar score in the whole study group supports the thesis of comparable neonatal results regardless of maternal age and parity (Bianco *et al.* 1996; Diejomaoh *et al.* 2006; Pawde *et al.* 2015).

The major limitations of the study include its retrospective nature and a small study sample. In addition, potential confounding factors, such as socioeconomic and educational status of the patients were not analyzed, because such data were not available. Moreover, contrary to many studies, the enrollment criteria included age at conception, not delivery, which significantly reduced the study group. Women of advanced age were not compared with younger pregnant population, as data about patients from tertiary care center could be misleading and cause information bias.

Nevertheless, this study provides evidence connecting primiparity with pregnancy complications in patients with advanced maternal age. This information could be valuable for women who consider postponing motherhood and helpful for couples during family planning. However, delayed child-bearing may also be caused by factors beyond woman's choice. Treatment options provided for couples who want to become parents but are unable to conceive spontaneously should include detailed data on possible pregnancy complications, as both advanced maternal age and assisted reproductive technologies are risk factors for adverse pregnancy outcomes (Johnson & Tough 2012).

As parity might be considered an additional potential risk factor for certain obstetric complications, each case of advanced maternal age should be managed individually. The older patients planning to conceive, especially for the first time, should be properly counseled and informed about possible perinatal problems.

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