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Preterm delivery risk factors in singletons born after in vitro fertilization procedures

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ABSTRACT

Objectives: Women delivering singletons after in vitro fertilization (IVF) procedures have a greater risk of preterm delivery (PD). The aim of our study was to analyze PD risk factors and to identify those that could possibly be prevented.

Study design: In our matched controlled study we analyzed 1127 singleton deliveries after IVF and transfer of fresh embryos performed at the University Medical Center Ljubljana between 1 January 2002 and 31 December 2010. For every delivery included in the study group we chose three consecutive controls matched by maternal age, parity and maternity hospital. The main outcome measure was PD (<37 weeks). Investigated variables were: previous PD (PPD), conization, pregestational diabetes mellitus, uterine anomaly, operation on the uterus, chronic renal disease, maternal age and parity, and body mass index (BMI). Variables investigated within the IVF group were: stimulation protocol, laboratory procedure, number of retrieved oocytes and number and quality of transferred embryos.

Results: The PD rate after IVF was 1.5 times higher than after natural conception (11.5% in the IVF group and 7.7% in the control group, $p < 0.001$). Conization and chronic renal disease were shown to be significant risk factors for PD in both the IVF group and the naturally conceiving controls. BMI > 30 was an important risk factor only in the IVF group (OR 1.86 (1.06–3.27) vs. 1.10 (0.67–1.80)) and PPD only in the controls (OR 1.83 (0.78–4.28) vs. 3.22 (1.55–6.67)). Among the investigated PD risk factors, an IVF procedure was shown to be the fifth most important one. On analyzing parameters of the ovarian stimulation and IVF procedure, no PD risk factor was identified.

Conclusions: IVF was shown to be a significant risk factor for PD. In the IVF population, BMI plays a far more important role in PD than in the fertile population. In our research PD reoccurrence in IVF group was less than expected, which could perhaps be explained by the surgical correction of gynecological pathology and, where necessary, its being combined with cerclage. The investigation of parameters related to the IVF procedure did not identify any risk factors for PD.

Introduction

Women delivering after an in vitro fertilization (IVF) procedure are at increased risk of preterm delivery (PD) [1–14]. Previous authors have reported up to two times higher incidence of PD in women conceiving singletons in an IVF procedure compared to naturally conceiving controls [1–5]. The PD rate is higher than in a fertile population, even a subfertile population needing 2 years for conception [9]. It is not clear whether the higher PD rate is a consequence of the IVF procedure itself or the characteristics of the infertile population [9]. Since there is a lower PD rate after a frozen-thawed embryo transfer, the hyperestrogenism after ovarian stimulation was considered to be one of the risk factors [4,11,12]. In previous reports, some pregnancy-related complications, such as placenta previa and placental abruption, are significantly more common among the IVF population and consequently contribute to PD [2].

Considering maternal factors for PD, we do know some risk factors from the general population, like advanced age, chronic renal disease, previous conization or previous PD. It is possible that these factors are more common in the IVF population or, on the other hand, that they perhaps act under different rules. It is known that women delivering after an IVF procedure are usually older than women conceiving naturally, but the influence of age is not enough to explain their higher PD rate [10]. Infertility per se also plays an important role in poor pregnancy outcome [15].

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Considering the findings of previous reports, our hypothesis was that factors from the IVF procedure as well as women's own risk factors for PD contributed to an increased rate of PD after an IVF procedure. This study was designed to identify the risk factors, especially those that could perhaps be minimized or prevented in the future.

The aim of our study was to examine PD risk factors connected to IVF procedures and to analyze woman's risk factors of PD in the IVF population and in naturally conceiving controls.

Materials and methods

Study design

In our matched controlled study we analyzed 1,127 singleton deliveries after IVF and transfer of fresh embryos performed at the University Medical Center Ljubljana between 1 January 2002 and 31 December 2010. For every delivery included in the study group we identified three consecutive controls matched by age, parity and maternity hospital.

In Slovenia all 14 maternity hospitals systematically collect data on maternal demographic characteristics, medical, gynecological and reproductive history, prenatal care, pregnancy, delivery, the postpartum period and neonates for each mother-infant pair, using the same definitions of variables and same form of medical record. Data are by default sent to the National Institute of Public Health of the Republic of Slovenia.

The study was performed in accordance with the Personal Data Protection Act of Slovenia. Considering that this is a retrospective analysis of anonymized data from the National Register, additional approval from the Medical Ethics Committee was not necessary.

Definitions

PD was defined as delivery before completed 37 weeks of gestation. Gestational age in the control group was determined in weeks since the last menstrual period, confirmed or corrected by early ultrasonography. In the IVF group it was determined as the number of weeks between the oocyte retrieval and the delivery plus two weeks.

Nulliparous women were women who had never given birth to a fetus of more than 22 weeks' gestation. Body mass index (BMI) was calculated from the pre-pregnancy weight.

Prior premature delivery (PPD) was regarded as spontaneous or induced vaginal delivery or elective cesarean section before 37 completed weeks of gestation. "Old primipara" was defined as a woman aged 33 and over at the time of her first delivery and "old multipara" as a woman aged 36 and over at the time of the observed delivery. Cold knife cone biopsy or loop electrosurgical excision procedure (LEEP) was regarded as conization. "Adnexal surgery" included all ovarian surgical procedures regardless of indication. The definition of uterine surgery included removal of uterine myomas and correction of uterine anomalies. Good quality embryos were all embryos with 8 or more cells transferred on day 3 or blastocysts without significant fragmentation transferred on day 5, whereas embryos in earlier development stages were classified as low quality embryos.

Multivariate logistic regression was used to identify independent risk factors for PD. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated with two-sided probability (p) values, and a p-value of <0.05 was considered as significant. Statistical analysis was performed using IBM SPSS Statistics, version 19 (IBM Corp, Armonk, NY).

Table 1
List of investigated risk factors according to their influence on PD: multivariate logistic regression.

Multivariate logistic regression for preterm delivery				
	OR	Lower	Upper	p-Value
Chronic renal disease	3.794	2.039	7.060	<0.001
Conization	2.723	1.830	4.052	<0.001
PPD	2.646	1.523	4.598	0.001
Uterine anomaly	2.675	1.160	6.167	0.021
IVF procedure	1.515	1.209	1.900	<0.001
Operation on uterus	1.418	0.822	2.446	0.210
BMI <18	1.426	0.907	2.242	0.124
BMI 18–30 (ref)	1			
BMI >30	1.317	0.912	1.900	0.141
Old primipara	1.085	0.864	1.363	0.481
Old multipara	0.863	0.602	1.237	0.422

Legend: IVF – in vitro fertilization, OR – odds ratio, CI – confidence interval, BMI – body mass index.

Results

The analysis included 1127 singleton deliveries in the IVF group and 3,381 singleton deliveries in the control group. In both groups the average maternal age was 33.43 ± 3.94 years and women were predominantly primiparous (72.3%).

The PD rate in the IVF group was significantly higher than in the control group, 11.5% and 7.7% respectively ($p < 0.001$).

Multivariate logistic regression of the study and control groups, showing the significance of PD risk factors, is presented in Table 1. The IVF procedure is shown to be a less important risk factor than chronic renal disease, previous conization, PPD and uterine anomaly.

Multivariate logistic regression for PD risk factors in the IVF and control groups is presented in Table 2. In the IVF group the

Table 2
Multivariate logistic regressions for PD risk factors.

Investigated preterm delivery risk factors				
	IVF group		Control group	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
PPD	1.83 (0.78–4.28)	0.166	**3.22 (1.55–6.67)**	**0.002**
Conization	**2.14 (1.02–4.49)**	**0.044**	**3.05 (1.90–4.88)**	**<0.001**
Uterine anomaly	–[a]		**4.54 (1.89–10.91)**	**0.001**
Operation on uterus	1.85 (0.89–3.86)	0.100	1.11 (0.47–2.61)	0.809
Chronic renal disease	**5.22 (1.74–15.67)**	**0.003**	**3.39 (1.57–7.33)**	**0.002**
Old primipara	1.03 (0.68–1.56)	0.877	1.07 (0.82–1.41)	0.604
Old multipara	1.25 (0.69–2.24)	0.451	0.70 (0.44–1.12)	0.138
BMI < 18	1.97 (0.84–4.62)	0.120	1.27 (0.74–2.18)	0.376
BMI 18–30 (ref)	1		1	
BMI > 30	**1.86 (1.06–3.27)**	**0.031**	1.10 (0.67–1.80)	0.707

Legend: IVF – in vitro fertilization, OR – odds ratio, CI – confidence interval, BMI – body mass index.
p-Value<0.05
[a] There were no cases of PD in women with uterine anomalies in the IVF group.