

Perinatal outcome of *in vitro* fertilization singletons – 10 years' experience of one center

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Abstract

Introduction: *In vitro* fertilization (IVF) singletons have a worse perinatal outcome than spontaneously conceived singletons, especially in terms of preterm birth and its complications.

Material and methods: An observational retrospective case control study was carried out. The study population consisted of 644 women in singleton pregnancies (336 IVF/intracytoplasmic sperm injection (ICSI); 308 controls) who delivered > 22 weeks of gestation at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland, between 2004 and 2014. Controls were initially matched by age and parity and drawn from the group of deliveries following each IVF delivery. Collected data included maternal characteristics, incidence of pregnancy complications, time and mode of delivery, and neonatal outcome at delivery.

Results: The two study groups were initially matched for age and parity and were also similar with regard to BMI and gestational weight gain. The IVF treatment increased the odds of having vaginal bleeding in the first trimester (OR = 1.68; 95% CI: 1.0–2.86), placenta previa (OR = 5.15; 95% CI: 1.1–33.9), preterm delivery (OR = 2.06; 95% CI: 1.16–3.68), newborn's low birth weight (OR = 2.27; 95% CI: 1.19–4.36) and elective cesarean section (OR = 2.39; 95% CI: 1.7–3.4).

Conclusions: The IVF singleton pregnancies have an increased risk of adverse perinatal outcome, among which prematurity remains the greatest problem. Therefore, they should be managed as high risk not only due to psychological reasons.

Key words: *in vitro* fertilization pregnancy, pregnancy complications, preterm delivery, *in vitro* fertilization obstetric outcome.

Introduction

Since the birth of Louise Brown in 1978, *in vitro* fertilization (IVF) technologies have developed rapidly and the accessibility to treatment has greatly improved. According to 2016 estimates the number of children born after assisted reproduction techniques (ART) exceeded 6.5 million. Available national birth cohorts show that the proportion of IVF infants ranges from 0.8% to 4.1% of all deliveries [1]. The latest European IVF Monitoring regarding ART procedures showed that almost

9000 IVF/intracytoplasmic sperm injection (ICSI) procedures were initiated in Poland in 2010 (only in centers reporting to the European Society of Human Reproduction and Embryology; ESHRE) – it means that with a success rate of over 30% at least 3000 Polish IVF babies are born each year [2]. Such numbers are no longer negligible, especially if the rate of ART pregnancies continues to rise worldwide.

Since the introduction of the method, various concerns have been raised regarding safety aspects of IVF pregnancies and children. Continuously growing evidence has shown that not only the rate of multiples after ART treatment contributes to poorer outcome. It has been widely proven that ART singletons alone have a worse perinatal outcome than spontaneously conceived singletons, especially in terms of preterm birth and its complications. Therefore, the knowledge of the causes of the poorer outcome seems to be crucial for all the clinicians dealing with IVF pregnancies.

Theoretically, the causes of the above are multifactorial. First of all there are factors unrelated to the treatment method, such as the characteristics of the population – age of the parents, cause of infertility and its probable genetic background. Secondly, there are various factors strictly linked to IVF technique – the method of fertilization (IVF or ICSI), culture media, cryopreservation methods or embryo selection methods. Finally, it is known that ovarian stimulation leads to the altered endocrine profiles of the patients during fresh embryo transfer procedures, which may influence implantation and early placentation [1, 3–6]. It is therefore very difficult to determine which of the above might really be the cause of the problem. However, recent evidence indicates that underlying subfertility seems to be very important, although it has often been omitted in analyses.

The primary objective of the study was to analyze the perinatal outcome of IVF singleton pregnancies in comparison to spontaneously conceived singletons, especially with regard to pregnancy complications, time and mode of delivery. The secondary outcome was to assess the relation of an underlying cause of infertility with pregnancy complications in IVF singletons.

Material and methods

An observational case control study was carried out. The analyzed population consisted of selected women in singleton pregnancies who delivered at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland, between 2004 and 2014 (tertiary medical center). The study group comprised of 336 patients who conceived by means of *in vitro* fertilization (IVF or ICSI). The control group consisted of 308 women who con-

ceived spontaneously (with no history of subfertility) and delivered within the same time period. Patients with a history of preterm birth, gestational hypertensive disorders or placental pathologies in the previous pregnancy were excluded from the study. Controls were initially matched by age and parity and drawn from the group of deliveries following each IVF delivery. All the included women delivered after completing 22 weeks of gestation. Preterm delivery was defined as birth within 23–36 + 6 weeks of gestation and low birth weight (LBW) as less than 2500 g at delivery. Pregnancies obtained by oocyte donation, frozen/thawed embryo transfer and those with major fetal anomalies were excluded from the study.

Collected data included maternal characteristics (age, parity, pre-pregnancy body mass index (BMI), gestational weight gain), incidence of pregnancy complications (first trimester bleeding, preterm deliveries, gestational diabetes, pregnancy-induced hypertension and preeclampsia, cholestasis of pregnancy, preterm premature rupture of membranes, placenta previa), time and mode of delivery with indications for cesarean section and neonatal outcome at delivery (birth weight and Apgar scores). In the IVF group maternal data also included the cause of infertility; however, due to the retrospective character of the study, such information was available only for 216 women out of 336. Therefore, calculations regarding the secondary outcome were performed only within the group of 216 patients. In order to determine the influence of the underlying subfertility, the study group was divided into five subgroups according to the indications for IVF treatment: tubal factor, male factor, anovulatory/polycystic ovary patients (ovarian factor), endometriosis and unexplained infertility. Due to the relatively small sample size of each of the five subgroups, pregnancy complications were analyzed collectively.

The authors have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects.

Statistical analysis

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 χ^2 test and exact Fisher's test for categorical variables. Statistical analysis was performed with the Mann-Whitney *U*-test for continuous variables. Logistic regression was used to calculate odds ratios (OR) and confidence intervals (CI) in order to estimate the association of pregnancy complications and cesarean section with IVF treatment. Statistical analysis was performed using Statistica

10.0 software with a p -value < 0.05 considered significant. All p -values were two-tailed and CI were calculated at the 95% level.

Results

Maternal characteristics

The two study groups were initially matched by age and parity (median parity in both groups equaled 1). The mean age in the IVF group was 33.9 ± 3.8 vs. 33.6 ± 3.8 years in controls ($p = 0.3$). The rate of primiparas was 88.4% (297/336) in IVF and 87.6% (270/306) in controls ($p = 1.0$). The groups were also similar with regard to BMI (22.7 ± 3.5 vs. 22.6 ± 3.9 kg/m²; $p = 0.7$), gestational weight gain (14.1 ± 6.9 vs. 14 ± 5 kg; $p = 0.9$) and the history of hypothyroidism (13.4% vs. 8.5%; $p = 0.08$). No data on smoking habits could be collected.

Pregnancy complications and neonatal outcome

The overall rate of pregnancy complications in IVF singletons was 46.4% in comparison to 40.2% ($p = 0.13$). The difference did not reach significance. However, the above result is biased by the fact that the study was performed in a tertiary center and the control group might not be a truly low risk population. Detailed information on selected pregnancy complications is presented in Table I. The IVF treatment increased the odds of having vaginal bleeding in the first trimester (OR = 1.68; 95% CI: 1.0–2.86), placenta previa

(OR = 5.15; 95% CI: 1.1–33.9) and preterm delivery (OR = 2.06; 95% CI: 1.16–3.68), especially prior to 32 weeks of gestation. The risk of remaining complications was not increased in the studied IVF singletons.

The mean gestational age at delivery was significantly lower in the IVF group: 38.1 ± 2.3 vs. 38.9 ± 1.6 weeks; $p < 0.001$. There was also a significant difference with regard to neonatal birth weight at delivery between the groups favoring controls: 3220 ± 635 g vs. 3402 ± 557 g. The odds ratio of LBW in IVF singleton pregnancies was 2.27 (95% CI: 1.19–4.36). Neonatal outcome was limited to Apgar scores. The majority of neonates from both groups were born in good general condition (no differences in 1st min Apgar scores). However, significantly fewer IVF babies were in a good general condition according to the Apgar score in the 5th min (8–10 points: 325/334 vs. 304/305; $p = 0.023$). There were 2 cases of stillbirth in the IVF group (delivery at 24 weeks and placental abruption at 31 weeks of gestation) and one case of early neonatal death due to extreme prematurity (delivery at 26 weeks). There was one case of stillbirth and one case of early neonatal death (delivery at 29 weeks due to preeclampsia and intrauterine infection) in the control group.

Causes of infertility and their relation to pregnancy complications

The analysis of the causes of infertility and their influence on gestational complications was

Table I. Selected pregnancy complications in IVF singletons and spontaneously conceived controls

Pregnancy complication	IVF (n = 336) n (%)	Controls (n = 308)** n (%)	P-value OR (95% CI)
First trimester bleeding	47 (13.99)	27 (8.8)	0.048 1.68 (1.0–2.86)
Preterm delivery < 37 weeks*	44 (13.24)	21 (6.81)	0.012 2.06 (1.16–3.68)
Preterm delivery 32–36 weeks	33 (9.85)	20 (6.49)	0.16 1.57 (0.85–2.91)
Preterm delivery < 32 weeks	11 (3.28)	1 (0.32)	0.013 10.4 (1.39–217.35)
Gestational diabetes	41 (12.2)	44 (14.37)	0.48 0.83 (0.52–1.35)
Gestational hypertension	26 (7.73)	20 (6.5)	0.65 1.2 (0.63–2.29)
Preeclampsia/eclampsia	5 (1.5)	4 (1.3)	1.0 1.15 (0.27–5.13)
Placenta previa	11 (3.2)	2 (0.65)	0.023 5.15 (1.1–33.9)
Intrahepatic cholestasis	6 (1.78)	3 (0.98)	0.5 1.85 (0.41–94)
PPROM	8 (2.38)	2 (0.65)	0.11 3.73 (0.73–25.63)

*Preterm delivery in IVF calculated for 335 women. **Due to missing data results calculated for 306 women.

Table II. Odds ratios for pregnancy complications in relation to the cause of infertility

Cause of infertility	Rate of pregnancy complications collectively (%)	OR for pregnancy complication OR (95% CI)
Endometriosis (<i>n</i> = 33)	42.4	1.1 (0.49–2.36)
Unexplained infertility (<i>n</i> = 53)	37.7	0.89 (0.47–1.69)
Ovarian factor (<i>n</i> = 51)	51	1.53 (0.81–2.89)
Tubal factor (<i>n</i> = 20)	40	1.0 (0.5–1.87)
Male factor (<i>n</i> = 29)	48.3	1.37 (0.6–3.12)
Overall OR of complications		1.29 (0.93–1.78)

limited to 216 cases. The subgroups were too small to show that any particular cause of subfertility had a significantly greater risk on overall rate of complications. Table II presents detailed analysis of odds ratios for particular subfertility types and pregnancy complications. The distribution of subfertility types in the groups of particular gestational complications was quite random, with the exception of placenta previa: almost half of the cases concerned women with endometriosis.

Mode of delivery

Sixty-nine percent of all IVF singletons were delivered by cesarean section in comparison to 44% of controls ($p < 0.01$). The indications for the operation varied significantly between the groups. The majority of CS in the IVF group was performed due to elective indications, with almost half of it only because of the history of IVF treatment, with no other obstetric indication. The odds ratio of elective CS in IVF singletons was 2.39 (95% CI: 1.7–3.4).

Discussion

Extensive data nowadays show that there is an increased risk of adverse perinatal outcome in IVF singleton pregnancies [7]. Earlier studies assessing the results of ART concentrated mainly on gestational age at delivery and newborns' birth weight, suggesting that the risk of preterm birth (PTB) and low birth weight (LBW) is higher among IVF singletons. In 1985 the first Australian data showing a worse perinatal outcome (higher rate of miscarriage and preterm delivery) after ART were published [8]. In 1999 Dhont *et al.* analyzed 3057 IVF singleton pregnancies and proved that the rate of preterm deliveries, LBW and very low birth weight (VLBW) was significantly higher [9]. Even after adjusting for maternal factors, such as ethnicity, age, parity, BMI, smoking habits and obstetric history, significantly higher rates of preterm delivery and LBW were still observed among IVF singletons [10, 11]. A systematic review of 25 case-controlled studies from 1985–2002 proved the earlier find-

ings – the calculated OR for delivery < 32 weeks of gestation was 3.27 (95% CI: 1.71–2.47) and for delivery at 32–36 weeks of gestation OR was 2.05 (95% CI: 1.71–2.47) [12]. A meta-analysis published in 2004 covering 12283 IVF singleton pregnancies, followed by two systematic reviews, once again underlined the higher risk for preterm delivery in the population of singleton IVF gestations [13–15]. Due to the change in IVF practice in the last couple of years (milder stimulation, shift to single embryo transfer (SET), better culture techniques), some of the newer evidence shows a similar outcome of IVF pregnancies in comparison to spontaneous conceptions. De Neubourg *et al.* did not find any significant differences in perinatal outcome when comparing IVF SET pregnancies in good prognosis patients with spontaneously conceived gestations [16]. Similar reports came from the United Kingdom and Japan [17, 18]. However, two recent meta-analyses once again proved the significantly higher risk of preterm delivery (both < 37 weeks with OR = 1.54 and < 32 weeks of gestation with OR = 1.68), lower birth weight (< 2500 g with OR = 1.65 and < 1500 g with OR = 1.93) and neonatal intensive care unit admissions (OR = 1.58) in IVF singletons. They also underlined that the causes of such adverse outcomes are poorly understood [1, 4]. Most recently, Qin *et al.* analyzed 52 cohort studies on 181741 IVF/ICSI pregnancies regarding adverse perinatal outcome. They again showed the higher prevalence of PTB/VPTB (very preterm birth) and LBW among IVF singletons [7]. The results of the present study are in accordance with the latest reports – the risk of preterm delivery and LBW was higher in IVF singletons.

An increased risk of pregnancy complications in IVF singletons is one of the suggested reasons for iatrogenic prematurity. Although the data are conflicting, it seems obvious that iatrogenic preterm delivery may be more frequent among IVF pregnancies, because such gestations are perceived differently not only by the patients, but also by physicians. Apart from prematurity the greatest accordance regarding other complications refers

to bleeding in the first half of gestation – the risk seems to be significantly higher among IVF singletons. Koudstaal *et al.* reported the rate of first trimester bleeding reaching 32% in comparison to 18.8% in controls. This problem might be due to luteal insufficiency or ovarian stimulation itself. However, it does not seem to depend on the type of fertilization (IVF or ICSI) [7]. In the present study the risk of bleeding during the first half of gestation was also significantly higher in the study group. According to other publications, first trimester bleeding might have also contributed to the higher rate of preterm deliveries among IVF singletons [19].

Placenta previa is another complication which seems to be related to the IVF treatment – the risk is increased especially in singletons [18, 20–23]. The meta-analysis from 2004 revealed a three-fold increased risk of placenta previa [13]. The most interesting paper regarding that subject was published by Romundstad *et al.* The authors described a group of 1349 women who had a history of both ART gestation and spontaneously conceived one – the risk of placenta previa increased four-fold after ICSI and six-fold after IVF (OR = 5.6). The risk was also three times higher in ART pregnancy in comparison to a natural gestation in the same woman, regardless of which was first in her life [24]. Although the risk is substantial, it is not fully understood. In most of the cases the risk is attributed to the transfer technique. In the present study the risk was similar to that described in the literature (OR = 5.15; 95% CI: 1.1–33.9). The recent meta-analysis combined all types of bleeding (first trimester, placenta previa, placental abruption) and estimated the odds ratio in IVF gestations to be 2.49 (95% CI: 2.30–2.69) [4].

The results referring to other pregnancy complications, such as gestational diabetes (GDM), gestational hypertension, intrahepatic cholestasis or preterm premature rupture of membranes, are very divergent or scarce. Sterling *et al.* reported an adjusted OR of 3.15 for the risk of GDM among IVF singletons among polycystic ovary syndrome (PCOS) patients [25]. A 2012 meta-analysis revealed that the odds of developing GDM were slightly greater in IVF singletons – OR = 1.48 (95% CI: 1.33–1.66). It also confirmed that the combined risk of developing PIH/PE is higher in IVF gestations (OR = 1.49; 95% CI: 1.39–1.59), although earlier findings were conflicting [4]. A recent cohort study from the CoNARTaS group revealed that the risk of hypertensive disorders was higher among all ART procedures and reached 5.9% in IVF singletons [26]. Only a few authors have tried to associate PIH with the cause of infertility and their results were contradictory: Isaksson *et al.* reported lower risk of PIH in IVF patients

with unexplained infertility, while Pandian *et al.* showed a higher risk of PIH and PE in theoretically similar infertile women [27, 28]. The risk of PIH/PE in the present study was insignificantly higher in IVF gestations, with no specific contribution of the cause of infertility. The risk of GDM in the studied material was similar to controls, with no visible influence of underlying subfertility. However, our results were biased by the fact that the study was performed in a tertiary center with a special outpatient clinic for GDM.

In the majority of published reports the rates of cesarean sections (CS) in IVF gestations are significantly higher than in spontaneously conceived ones and they vary between 21.2% and 47.2%, with ORs from 1.27 to 3.6 [4, 9, 12, 21]. In comparison to the literature, the rate of operative deliveries in IVF singletons in our center is unreasonably high – 69% vs. 44% in controls. This fact can be partially explained by the recommendations of the Polish Gynecological Society, which suggested that the patient in IVF singleton gestation may have an influence on the decision regarding mode of delivery [29]. In the present study the majority of CS in IVF group were performed due to elective indications, of which the history of IVF treatment only contributed to 42.4%. The problem of high rates of operative deliveries seems to be related to greater anxiety of both the parents and the physician, as none of them want to witness delivery complications influencing the future health of a long awaited child.

There are only a few papers mentioning the cause of infertility and its relation to pregnancy complications. Nevertheless, there is increasing evidence that the causes of infertility are independent risk factors, though not the only ones, of obstetric complications and an adverse perinatal outcome, even without the addition of IVF treatment. Pandian *et al.* related unexplained infertility with greater risk of preeclampsia and placental complications [27]. Others reported fewer preterm deliveries in IVF singletons where only male factor was present [21, 30, 31]. There are also publications where no association between the etiology of infertility and obstetric outcome was found [27, 32]. The study by Kuivasaari-Pirinen *et al.* suggested that the risk of placenta previa was higher in women with endometriosis and male factor, the risk of preterm birth higher for endometriosis and anovulation, while small for gestational age (SGA) was more often diagnosed in cases with male factor and unexplained infertility [33]. Probably women with endometriosis are the best studied group undergoing IVF. The majority of reports are in agreement that patients with diagnosed endometriosis are at greater risk of preterm delivery and SGA, placental complications, antepartum

bleeding and cesarean section [34, 35]. The most recent study by Benaglia *et al.* proved once again the higher risk of placenta previa in IVF singleton pregnancies among women with endometriosis (OR = 4.8), but the risk of PTB in their paper was similar to controls [36]. The results of the present study did not prove such an influence of endometriosis or any other cause of infertility on the outcome due to the small sample size. Nevertheless, half of the cases of placenta previa in the IVF group were diagnosed in women with endometriosis, which seems worth noting. A recent systematic review regarding the problem of adverse perinatal outcome in IVF singletons provided moderate evidence that subfertility itself increases the risk of preterm delivery. The meta-analysis on ART and non-ART siblings showed a higher risk of preterm birth in the ART group [1]. Similar results were presented by Romundstad *et al.* in a Norwegian study, where the increased perinatal risk was attributed to the factors that led to infertility [3].

In conclusion, IVF singleton pregnancies have an increased risk of adverse perinatal outcome, among which prematurity remains the greatest problem. Therefore, they should be managed as high risk not only due to psychological reasons. It should be acknowledged that the population of IVF patients is very heterogeneous, and therefore the influence of the underlying subfertility and treatment methods on perinatal outcome is inevitable. Since the majority of national records lack information on the cause of infertility, it continues to be the least studied problem and requires further studies.

Conflict of interest

The authors declare no conflict of interest.

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