Perinatal outcome of singleton pregnancies following in vitro fertilization

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Summary

Purpose of investigation: To determine whether in vitro fertilization/intracytoplasmatic sperm injection (IVF/ICSI) singleton pregnancies are at increased risk for maternal and fetal complications than spontaneous singleton conceptions. *Materials and Methods:* The pregnancy outcome of 634 singleton pregnancies after IVF/ICSI delivered at the Clinic for Gynecology and Obstetrics during the period January 2006 to January 2010 were compared to 634 matched singleton controls, matched one by one by age, parity, education, and body mass index (BMI). Differences in pregnancy outcomes between the groups were assessed using Student's t-test with Yates correction for continuous variables and Chi-squared test for categorical variables. *Results:* The mean gestational age at delivery of the IVF group was 38.13 ± 1.72 weeks, slightly shorter than spontaneously conceived singletons at 38.65 ± 1.79 weeks. The diagnosis of gestational diabetes mellitus (GDM) was frequently made in the IVF group (11.82% vs 8.35%, t = 2.052, $p < 0.05$). Total preterm delivery rate of IVF pregnancies was 9.30%, significantly higher than the controls 5.85% (t = 2.33, $p < 0.05$), especially at the 30-32 weeks gestation period. The predominant mode of delivery after IVF pregnancy was cesarean section (80.75% vs 31.38% at spontaneously conceived, t = 17.71, $p < 0.001$), while vaginal route was the choice for naturally originated pregnancies 68.6% vs 19.24% ($p < 0.01$). No differences were found in the average birth weights, LBW, VLBW, SGA, and LGA regarding the pregnancy origin. Perinatal mortality rates were comparable among singletons with different pregnancy origin. *Conclusions:* Singletons from IVF/ICSI pregnancies have poorer perinatal outcome associated with higher rates of cesarean sections, preterm birth and prematurity, fetal malpresentation (breech presentation), and the occurrence of maternal GDM in pregnancy.

Key words: In vitro fertilization; Singletons; Pregnancy; Perinatal outcome; Cesarean section.

Introduction

Since the first child was born in 1978 after fertility in vitro treatment, the number of assisted pregnancies has increased steadily [1] and currently accounts for 1%-4% of all conceptions [2]. Much interest has been dedicated to the safety of assisted reproduction technology (ART) [3].

The use of in vitro fertilization (IVF) has shown to be associated with various pregnancy and neonatal problems, most significantly due to the high rate of multiple births. Multiple pregnancies after IVF account for 20%-25% [4].

Numerous studies at first indicated poor perinatal outcomes for assisted twin compared to spontaneous twin conceptions [5-7]. The increased risk for adverse perinatal outcome in IVF pregnancies cannot be entirely explained by the incidence of multiple births. The first indication that assisted singletons may also have poorer outcomes appeared in 1985 as reported by an Australian IVF collaborative group [8]. In numerous studies, it has been demonstrated that singletons, besides multiples, have a poorer outcome, compared to singletons in the general population [7, 9-11]. The cause of this risk is not fully understood, but for safety reasons it is important to elucidate this question.

The explanations include various categories such as the IVF laboratory procedures [9], differences in maternal characteristics as age, parity, smoking, obesity [7], type of infertility and duration, presence and type of ovarian stimulation, and presence of twin pregnancies spontaneously reduced to singletons (vanishing twins) [6, 12].

Unadjusted analysis suggested a two-fold increased risk of preeclampsia, placental abruption, cesarean section, and operative delivery, and five-fold increased risk of placenta previa in spontaneous singleton pregnancies in women with a history of infertility compared with the general population [13-16].

Several studies [17, 18] have indicated that the risk of perinatal mortality is increased in singleton pregnancies achieved after ART. Significantly higher rates of preterm delivery and low birth weight (LBW) were observed for IVF singletons [16], even after adjustment for maternal age, parity, duration of infertility, smoking, and body mass index (BMI).

Babies born after intracytoplasmatic sperm injection (ICSI) procedures have demonstrated to have a higher incidence of both autosomal and sex chromosome abnormalities, but surprisingly similar to those reported after classic IVF procedure [5].

The present authors investigated the influence of ART procedures on perinatal outcome by comparing the group of singleton ART pregnancies and the group of spontaneously-conceived singletons pregnancies.

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Table 1. — *Maternal characteristics*.

Characteristic		IVF/ICSI group (n = 634) No.	%	Control group (n = 634) No.	%	Significance
Average age (years)		36.450 ± 4.218		35.391 ± 4.174		NS
Previous spontaneous abortions		54	8.51%	27	4.26%	$\chi^2 = 10.73$; $p < 0.01$
Ectopic pregnancy		39	6.15%	16	0.33%	$\chi^2 = 12.08$; $p < 0.01$
Education	low	69	10.88%	85	13.40%	NS
	moderate	267	42.11%	273	43.06%	NS
	high	284	44.79%	274	43.21%	NS
BMI (kg/m^2)		23.1 ± 4.1		23.7 ± 3.7		NS

BMI: body mass index; *p:* probability; NS: no significance.

Table 2. — *Complications during pregnancy*.

Categories	IVF group No.	%	Control group No.	%	Significance
PIH	100	15.770%	74	11.670%	NS
PE	11	1.730%	6	0.950%	NS
GDM	75	11.820%	53	8.350%	t = 2.052, $p < 0.05$
Placenta previa	4	0.630%	0	0.000%	NS
Placental abruption	4	0.630%	2	0.315%	NS
PPROM	17	2.680%	11	1.735%	NS
PROM	37	5.830%	24	3.785%	NS
Maternal blood transition	6	0.950%	5	0.750%	NS

PIH: pregnancy-induced hypertension; GDM: gestational diabetes melitus; PE: pre-eclampsia; PPROM: premature preterm rupture of membranes; PROM: premature rupture of membranes; p: probability; NS: no significance.

Materials and Methods

The obstetrical outcome of 634 consecutive singleton pregnancies after ART, delivered at the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, from the period January 2006 to January 2010 were compared to 634 matched controls (spontaneously conceived singletons), matching one to one by age, education, parity, time, and place of delivery. Only pregnancies with duration of more than 26 weeks were included. The Serbian definition of birth comprises all live born and stillborn babies delivered after 26 weeks of gestation.

The study group was formed by 634 primiparous women delivered at the Clinic, with singleton ART pregnancy achieved with controlled ovarian stimulation with a complete documentation of ART procedure (IVF or ICSI), and infertility history treatment. The control group was formed by 634 patients without infertility problems, that spontaneously conceived a singleton pregnancy and delivered at the same hospital within the study period. The controls and the cases were matched one to one for age, parity, education, body mass index (BMI), site, and time of delivery (within one month).

Those pregnancies resulting from an oocyte donation, cryopreserved cycles or conceived as twin but continued as singleton, were excluded from the study (26 pregnancies). Details on patient demographics, life style, and pregnancy outcome were collected by chart review and patients' questionnaire. All pregnant patients with incomplete or insufficient data on the course of pregnancy and delivery were excluded from the study, as well as patients without appropriate control after IVF/ICSI procedure. The gestational age for the ART group was calculated as the duration between the date of embryo transfer and delivery plus fourteen days; for spontaneous conceptions the gestational age was based on the last menstrual period or estimated at the first trimester ultrasound scan.

Maternal complications' pathology PIH (pregnancy-induced hypertension), gestational diabetes mellitus (GDM), preeclampsia, eclampsia, placenta previa, PROM, PPROM (preterm/premature rupture of membranes), need for cerclage application, and placental abruption were recorded. Data concerning fetal pathology as intrauterine fetal demise, chromosopathy, presence of congenital malformations, IUGR (intrauterine growth restriction), and macrosomia were encountered. Complications during labor, mode of delivery, gestational age, birth weigh and Apgar scores, neonatal complications, admission to neonatal intensive care unit (NICU), and perinatal mortality were compared between the groups.

Low birth weight (LBW) and very low birth weight (VLBW) were defined as birth weight < 2,500 g and < 1,500 g, respectively. Preterm and very preterm deliveries were defined as such before 37 and 32 completed gestational weeks, respectively. Small for gestational age (SGA) and very small for gestational age were defined as < 10th and < 23rd percentile for gestational age.

In controlled ovarian hyperstimulation, a flare-up or down-regulation protocol was used with gonadotropin-releasing hormone (GnRH) agonists and recombinant follicle-stimulating hormone (rFSH) or highly purified-human menopausal gonadotropin (HP-HMG). When at least of half of the dominant follicles reached 18 mm in average diameter, human chorionic gonadotropin (hCG) was administered and oocyte retrieval was performed after 34 to 36 hours. Conventional IVF and ICSI procedures were performed according to standard procedures. Embryo transfer was performed on the second or third day after oocyte retrieval. Luteal support consisted of micronized oral/vaginal progesterone 600 mg per day or muscular progesterone 250 mg on every second day.

The authors performed a univariable analysis, using Chi squared test for categorical outcome variables and Student's t-test for continuous outcome variables. A p value of < 0.05 was considered significant. Linear regression was applied for the analysis of birth weight, with adjustment for prognostic factors. The Institutional review board approved the study.

Results

A total of 634 IVF/ICSI singletons and 634 consecutive spontaneously conceived singletons were compared during the 2006-2010 period. Baseline patients' characteristics are presented in Table 1. The average age, education, parity, and BMI did not differ between studies and controls; however, regarding prior obstetric history, there was a higher risk of a spontaneous abortion (8.51% in the IVF group vs 4.258% in the controls) or ectopic pregnancy, if the pregnancy was of IVF origin. This differ-

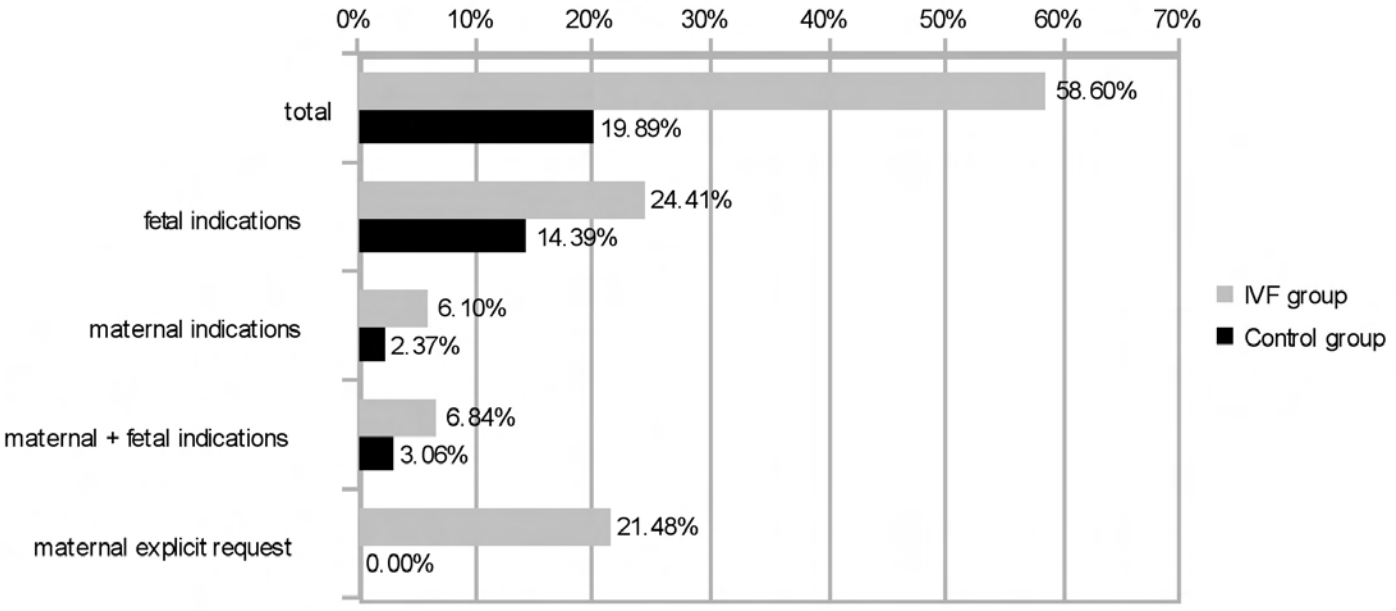

Figure 1. — Indications for elective cesarean section.

The significant difference between groups in a number of pregnancies delivered through elective cesarean section is obvious ($p < 0.01$) and the most contributing category is on mother's explicit request.

ence was highly significant ($\chi^2 = 10.73$, $p < 0.001$ for spontaneous abortion, $\chi^2 = 12.08$, $p < 0.001$ for ectopic pregnancy) and was expected because the IVF is an infertility problem tool (Table 1).

Of the 634 singletons pregnancies, 351 occurred after classic IVF procedure (55.35%) and 283 after ICSI fertilization (44.63%).

Complications in pregnancy (pregnancy-induced hypertension, pre-eclampsia, eclampsia, PPROM, PROM, placenta previa, and placental abruption) were equally distributed between groups, with one interesting exception regarding GDM (Table 2). About 75 women (11.82%) in the IVF group were diagnosed with GDM with oGTT (oral glucose tolerance test), while only 53 (8.35%) in the spontaneously-conceived group had GDM ($t = 2.052$, $p < 0.05$), which was statistically significant.

The causes of infertility in the IVF group were tubal pathology (28%), male factor (22%), ovarian etiology (15%), unknown origin (14%), and other causes (21% - combined, cervical, uterine, and immunological).

The management of ART pregnancies included singletons and seems to differ from that of spontaneously-conceived with singletons. The mode of delivery, indications, complications, and fetal presentation are listed in Table 3. Malpresentation or malposition of the fetus (excluding cephalic vertex occiput anterior presentation) was more common to occur in the IVF group, with a statistically significant difference (80 cases (12.6%) vs 56 cases (8.83%, $t = 2.508$, $p < 0.05$). Upon further analysis, malpresentation was divided into the categories breech presentation (9.46% of IVF vs 4.42% at controls), occipito-posterior position (1.26% vs 3.78%), and others (1.89% of IVF vs 0.63% of controls), included brow presentation, face presentation, vertex presentation, transverse lie). Among 634 singleton fetuses after ART, 60 (9.46%) were breech, compared with 28 (4.42%) among spontaneously-conceived pregnancies ($t = 3.533$, $p < 0.001$). Among ART pregnancies, there was no difference in the risk of breech presentation between the IVF group and the group conceived with ICSI procedure.

The rate of cesarean section were high in both groups (80.75% of IVF group vs 31.38% of controls), with almost two-thirds of pregnancies in the IVF group ending in an elective procedure (highly-significant difference, $t = 17.71$, $p < 0.001$). The large number of cesarean sections in both groups was elective, and the rate of emergency sections was 22.08% of IVF vs 11.58% of controls. Combined with the higher rate of malpresentation and breech in IVF group, the probable prominent contributing factors included the actual increase in complications predisposing operative delivery or a component of iatrogenic interventions. Most pregnancies of spontaneous origin ended up in vaginal delivery mode 68.6%, with only 19.24% of the IVF group delivered vaginally ($p < 0.01$). Also, the vaginal operative delivery by forceps, was almost exclusively performed in the controls (1.25% of controls vs 0.157% only one case of IVF group, $t = 2.34$, $p < 0.01$).

Since 80% of controls were delivered through vaginal route, the frequency of soft-tissue injuries expectancy was higher in terms of cervical and vaginal injuries and perineum ruptures than in the IVF group, with a high statistical significance.

Since the contribution of elective cesarean section rate is most evident in the high rate of pregnancies in the IVF group, the indications are listed in Figure 1. Similar data

Table 3. — *Delivery mode and complications during labor*.

Categories		IVF group No.	IVF group %	Control group No.	Control group %	Significance
Malpresentation		80	12.61%	56	8.83%	t = 2.508, $p < 0.05$
Operative vaginal delivery		1	0.16%	8	1.26%	t = 2.34, $p < 0.05$
Vaginal delivery		122	19.24%	435	68.61%	t = 17.75 , $p < 0.01$
	elective	372	58.67%	126	19.87%	t = 14.145, $p < 0.01$
Cesarean section	urgent	140	22.08%	73	11.51%	t = 5.332, $p < 0.01$
	total	512	80.75%	199	31.38%	t = 17.71, $p < 0.01$
Injury of soft tissues	cervix	32	5.04%	117	18.45%	t = 8.22, $p < 0.01$
	vagina	10	1.57%	46	7.22%	t = 4.9075, $p < 0.01$
	labii	1	0.16%	3	0.47%	NS
	perineum	10	1.57%	35	5.52%	t = 3.803, $p < 0.01$

p: probability, NS: no. significance.

Table 4. — *Perinatal-neonatal outcome*.

Characteristics		IVF group No.	IVF group %	Control group No.	Control group %	Significance
Average gestational age (weeks)		38.13 ± 1.7276		38.648 ± 1.7976		NS
Preterm labor (weeks)	< 32	20	3.15%	11	1.74%	t = 2.33, $p < 0.05$
	< 34	12	1.89%	10	1.58%	NS
	< 37	27	4.26%	16	2.52%	NS
	Total	59	9.30%	37	5.85%	NS
Average birth weight at delivery (gr)		3214 ± 579.4		3294 ± 549.23		NS
Birth weight (gr)	VLBW (< 1500)	10	1.58%	5	0.79%	NS
	LBW (< 2500)	51	8.04%	38	6.00%	NS
Still birth		6	0.95%	3	0.47%	NS
Early neonatal death		2	0.32%	2	0.32%	NS
Perinatal mortality		8	1.26%	5	0.79%	NS
Admission to NICU		55	8.67%	42	7.09%	NS
SGA (< 10th percentile)		23	3.62%	18	2.84%	NS
LGA (> 90th percentile)		27	4.26%	39	6.15%	NS

VLBW: very low birth weight; LBW: low birth weight; NICU: neonatal intensive care unit; SGA: small for gestational age; LGA: large for gestational age; p: probability; NS: no significance.

is registered in categories of fetal indications 24.41% of the IVF group vs 14.39% of the controls, of maternal indications 6.10% vs 2.370%, of category maternal and fetal indications altogether 6.84% vs 3.06%, and mothers' explicit request was only 21.48% in the IVF group. The indication that contributed mostly to the increased rate of elective cesarean sections in the IVF group was "explicit mothers' request", since the other indications presented with similar percentages.

The data on neonatal i.e. perinatal outcome are presented in Table 4. The mean gestational age at delivery of the IVF group was 38.13 ± 1.72 weeks, and was slightly shorter than the spontaneously conceived singletons 38.65 ± 1.79 weeks, but with no significance. Total preterm delivery in the IVF group in 9.30% was substantially higher than the controls in 5.85%, with significance (t = 2.33, $p < 0.05$). Upon further analysis, when total preterm delivery rate was divided into categories of different gestational age (< 32 weeks of gestation, < 34 weeks of gestation, < 37 weeks of gestation), the difference between the groups became insignificant however, if the time interval of the preterm pregnancy duration less than 32 weeks of gestation, it was divided into two periods, first from 30-32 weeks of gestation and the second less than 30 weeks of gestation, and the difference therefore became obvious and highly-significant 2.52% (16 cases) of the IVF group and 0.47% (three cases) in the controls (t = 3.00, $p < 0.01$).

The mean birth weight in the IVF group was 3,214 ± 579.4 g, lower than those of the controls 3,294 ± 549.3 g, but with no statistical significance. The rates of VLBW infants with less than 1,500 g (1.577% of IVF vs 0.788% of controls) and LBW less than 2,500 g (8.044% of IVF group vs 5.999% of controls), were comparable. Also, the prevalence of SGA, defined as birth weight less than 10th percentile for gestational age (23 cases; 3.62% of IVF group vs 18 cases; 2.839% of controls) and LGA with a birth weight more than 90th percentile for the appropriate gestational age were also similar between groups.

Neonatal admission to NICU accounted for 55 infants in the IVF group and 42 cases in the control group. There were six stillbirths in the IVF group including one-sudden fetal death at 39 wg, weight 3,900 g, with umbilical knot accident; one with a weight 2,200 g, at 34 wg, with hydrothorax; one at 31 wg, weight 1,250 g for chorioamnionitis; one at 31 wg, weight 1,400 g, with placenta previa for abruption; one at 35 wg, weight 1,450 g, with severe IUGR; one at 38 wg, weight 2,700 g, for placental abruption. Two neonates died during the early neonatal period, the first delivered at 32 wg, weight 700 g with severe IUGR due to perinatal asphyxia, and the second delivered at 26 wg, weight 640 g with placental

abruption. At controls, the three cases of stillbirth included infants delivered at 27 wg, weight 1,000 g, and two in term pregnancies at 39 wg weight 2,650 g for unknown reasons and at 37 wg, weight 2,400 g with IUGR and multiple anomalies. Two live born infants died after birth due to complications of acute asphyxia with instrumental forceps delivery and one case after prolonged pregnancy and prolonged delivery.

Only one case of chromosopathy included Klinefelter syndrome 47XXY, was recorded in the whole study in the IVF group and was detected prenatally through amniocentesis. Congenital malformations were present in six cases in the IVF group (two cases of intrabdominal cysts in females, heart anomaly (one case), hydrothorax (one case), right hand anomaly (one case), and isolated ventriculomegaly (one case); all except hydrothorax at stillbirth fetus, compatible with postnatal life. Of the spontaneously-conceived infants, five showed evidence of malformations including two cases of torticollis, one case of multiple anomalies, and two cases with heart malformations. Perinatal mortality accounted for eight cases (1.26%) at IVF group and five cases (0.788%) of controls, assuming the categories of intrauterine death after 26 wg and neonatal death within 28 days of birth.

Discussion

The first indication that assisted singleton pregnancies, besides multiples, have poorer pregnancy outcome compared to spontaneously conceived ones, appeared in 1985 by an Australian IVF collaborative group [8]. At that time, it was not clear how much the above reasons were related to assisted reproduction procedure or to confounders, such as maternal age and parity.

Several matched cohort studies have since confirmed those findings regarding differences between assisted singletons and spontaneously conceived ones [19-22]. However, a number of studies, mainly formed one center, showed an opposite trend [23, 24], but the problem of most studies was the selection of controls, the heterogeneity of assisted reproductive group, small sample size, and different parameters for pregnancy outcome.

Singletons conceived after assisted fertilization are at higher risk of low birth weight, preterm delivery, and perinatal death than spontaneously-conceived singletons, suggesting that the technology and not the factors contributing to infertility might cause differences in risk [7, 9, 25, 26].

Increased risk of adverse pregnancy outcome after IVF or ICSI procedure, opposite to the previous theories, may be the result of treatment-related factors (in vitro culture conditions, or hormonal stimulation) as well as patient-related factors (type of infertility, duration of infertility, other characteristics of subfertile patients) [27].

Romundstad *et al*., in their recent study found no significant differences in birth weight and perinatal outcome parameters when compared to sibling singletons born in 2,500 women who had conceived one child spontaneously and another child with IVF. These results suggest that patients' factors (contributing to infertility), rather than IVF technology, are responsible for the less favorable outcome after IVF [25].

The mean maternal age, grade of education, BMI, and parity were comparable between groups but there were almost twice as many women in the IVF/ICSI group with history of spontaneous abortion (8.51% IVF group vs 4.258% controls, $p < 0.01$) and ectopic pregnancy (6.15% IVF group vs 0.32% controls, $p < 0.001$). The difference is significant and expected, in favor of infertility patients, because these patients were in demand for IVF technology as the last option to solve their infertility problems.

IVF singletons do not have a greater risk of maternal complications in categories of pregnancy-induced hypertension (PIH), pre-eclampsia, placenta previa, PPROM, PROM, anemia, and the need for blood transfusion in the study, as in many studies [12, 28]. Interestingly, there is a significant difference in the term of GDM if the IVF/ICSI treatment is present (11.82% IVF group vs 8.35% controls, $p < 0.05$). The present authors found no studies reported with similar findings. These results need to be tested on larger samples in multicentre studies. Perhaps, pregnancy management was more meticulous in the IVF group than in the controls, with better diagnosis and more required oGTT performance, which resulted with an obvious difference.

The risk of developing pre-eclampsia and pregnancy-induced hypertension is increased in ART pregnancies reported by Shevell *et al*., contrary to the present study results [29]. Obstetric complications as pre-eclampsia, placental abruption, and placenta previa occur more frequently in IVF singleton pregnancies compared with spontaneous ones [16-18]. Confirmation of this finding has no support in the present research.

Fetal position/presentation was unfavorable in 12.61% of cases in the IVF group vs 8.83% in the controls with an obvious significant difference ($p < 0.05$) with a dominance of breech presentation. Among 634 singletons after ART, 9.46% were breech presentation compared with 4.42% among spontaneously conceived ones. ($t = 3.533$, $p < 0.001$), the most frequent malposition in both groups. The other fetal malposition/malpresentation are similarly distributed in both groups, but with no significance.

There is some evidence that breech presentation occurs more often in pregnancies following assisted fertilization in studies of Ombelet *et al*., and Romundstad *et al*., but it is unclear to which degree the excess risk is due to technology itself or to the other factors associated to assisted fertilization [30, 31]. The etiology of breech presentation still remains unclear, but it is linked to prematurity, a first pregnancy, advanced maternal age, placenta previa, uterine anomalies, and a previous breech presentation [32].

The obstetrics management of ART pregnancies seems to differ from that of spontaneously conceives ones, and there is a growing tendency to treat them as "special" pregnancies. ART deliveries are more likely to be

induced, and the rate of cesarean sections, especially elective, is considerably higher [33-36].

About 80% of ART pregnancies in the present study were delivered through cesarean section, opposite to 31.38% pregnancies of spontaneously-conceived group, with substantial difference ($p < 0.001$). The frequency of cesarean section in the current hospital is about 35% in the general population. More than two-thirds of all number of ART cesarean sections are elective, while at controls that percentage reached about half in all. The possible explanation of the difference may include the different management of IVF pregnancies and allowance of "mothers' explicit request" as indication for elective cesarean section in IVF pregnancies. Along with relative indication "pregnancy after IVF", these are the most contributing factors to a high rate of elective cesarean sections. For most couples with fertility problems, there is also a psychological burden, accompanied with the substantial economic burden for infertility treatment. These factors may also explain why their pregnancies are subjected to closer surveillance and different management by obstetricians than spontaneously conceived pregnancies.

The optimal mode of delivery for breech presentation is controversial. Indications for cesarean sections are typically diverse; some will be performed as an elective procedure, whereas others may be due to an acute obstetric situation. Romundstad *et al*., found that the rate of elective cesarean section for breech deliveries was considerably higher in ART group, and the rate of acute cesarean sections for cephalic deliveries was also higher [31]. These findings indicate that ART pregnancies are a target for more active obstetric management. This need for intervention is probably one of the contributing factors to a slightly shorter length of ART gestation.

The average duration of pregnancy is similar, regardless of origin and is 38.684 ± 1.79 weeks for spontaneously-conceived while a little shorter for IVF group, 38.13 ± 1.72, weeks, but when total deliveries are divided into the categories of term and preterm delivery, the difference becomes obvious. The event of preterm delivery is more likely to occur in IVF pregnancies (9.30% of IVF group vs 5.85% of controls, $p < 0.05$). Further analysis of preterm labor discovered that the significant difference between the groups is in those delivered in the interval from 30 to 32 weeks of gestation - 2.52% (16 cases) of IVF group and 0.47% (three cases) of controls (t = 3,00, $p < 0.01$).

Four meta-analyses of perinatal outcomes in singleton pregnancies found that compared with spontaneously conceived singletons in the general population, those born after IVF/ICSI are about twice as likely to be born preterm, are nearly three times more likely to weigh less than 1,500 g, and have 50% higher risk of being SGA [7, 9, 25, 37].

No differences were recorder in the frequency of LBW < 2,500 g and VLBW < 1,500 g in the present study. This is consistent with other studies referring data from single hospital centers [24, 34, 38]. Some previous studies found an increase risk for VLBW < 1,500 grams among the singletons conceived after IVF, but the present study does not uphold those findings [9, 10, 39].

Also, the incidence of SGA and large for gestation age (LGA) do not differ according to the pregnancy origin. The term singletons were more likely to have a low birth weight, consistent with previous reports of LBW in children conceived with ART [3, 36, 40, 41]. Wang *et al*., 1994 [42] suggested that ART pregnancies have increased risk for placental insufficiency and IUGR. On the contrary, the current study results, showed comparable rates of infants classified as SGA (< 10th percentile) in IVF and in spontaneously-conceived pregnancies, are similar to recent single center studies [43, 44].

In conclusion, singletons from IVF/ICSI pregnancies have poorer perinatal outcome associated with higher rates of cesarean sections, preterm birth and prematurity, fetal malpresentation (breech presentation), and the occurrence of maternal GDM in pregnancy, compared with singletons spontaneously conceived.

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