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ORIGINAL ARTICLE

Assessment of perinatal outcomes of pregnancies conceived by *in vitro* fertilization-intracytoplasmic sperm injection

[1]Alper KAHRAMAN
[2,3]Fırat TÜLEK
[4]Bülent BERKER

[1]Department of Obstetrics and Gynecology, Haseki Training and Research Hospital, İstanbul, Turkey

[2]Department of Obstetrics and Gynecology, Memorial Ataşehir Hospital, İstanbul, Turkey

[3]Department of Midwifery, Üsküdar University Faculty of Health Sciences, İstanbul, Turkey

[4]Department of Obstetrics and Gynecology, Ankara University Faculty of Medicine, Ankara, Turkey

ORCID ID
AK : 0000-0002-1689-2782
FT : 0000-0003-1668-8746
BB : 0000-0001-7346-7128

ABSTRACT

Objective: The objective of this study is to compare maternal and perinatal outcomes of singleton pregnancies obtained by *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment and spontaneously conceived singleton pregnancies.

Material and Methods: Patient records of women conceived by IVF/ICSI and spontaneously conceived women that delivered in Ankara University, Department of Obstetrics and Gynecology after the 24th gestational week and whom the postnatal follow-ups of the infants were conducted in Ankara University, Department of Pediatrics, were retrospectively evaluated. Study group consists of 180 women with singleton IVF/ICSI pregnancies were. Control group included 624 spontaneously conceived women with singleton pregnancies that gave birth within the selected study period.

Results: Median maternal age of the IVF/ICSI group was found significantly higher than the control group (p=0.031). A significantly higher incidence of hypertensive complications in pregnancy was found in IVF/ICSI group (p=0.001). Incidence of gestational diabetes mellitus was found significantly higher in IVF/ICSI group (p<0.001). Cesarean section rates were significantly higher in IVF/ICSI group in comparison with spontaneously conceived pregnancies (p<0.001). Preterm delivery rate is significantly higher in IVF/ICSI group (p<0.001). Infants born by IVF/ICSI pregnancies were showed a significantly higher rate of neonatal intensive care unit requirement in comparison with infants born by spontaneously conceived pregnancies (p<0.001). However, the statistical significance of the difference was observed to disappear after adjusting the data for gestational week at birth (p=0.161). Secondary sex ratio was found significantly lower in IVF/ICSI pregnancies (p=0.001).

Conclusion: Singleton pregnancies conceived by IVF/ICSI present higher risk for some adverse perinatal outcomes and should be followed accordingly.

Keywords: *In vitro* fertilization, *in vitro* fertilization/intracytoplasmic sperm injection, perinatal outcome, singleton.

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Correspondence: Alper KAHRAMAN, MD. Haseki Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, İstanbul, Turkey.
Tel: +90 537 287 37 30 **e-mail:** alper.k@hotmail.com

INTRODUCTION

Infertility is described as failure to conceive after 12 months of unprotected sexual intercourse. Chances of conception in healthy couples are accepted as 57% in the first 3 months, 85% within 1 year, and 93% in 2 years.[1] Fecundability is described as rate of live births in a cycle and estimated to be 25% in healthy couples. Rest of the reproductive age couples, namely, 10–15%, is accepted as infertile.[1]

Contemporarily, worldwide trend toward a higher childbearing age partially counterpoised by developing assisted reproductive techniques. Although increasing number of couples is conceiving by assisted reproduction, studies about perinatal mortality and morbidity are reporting conflicting and controversial findings. Some authors describe higher rates of various pregnancy complications such as gestational diabetes, hypertensive disorders, preterm delivery, placenta previa, low birth weight (LBW), and increased rates of cesarean deliveries in women conceived by assisted reproduction.[2–7] However, some studies indicate lower perinatal mortality rates in comparison to spontaneously conceived pregnancies.[8] These findings were partly attributed to higher age of women conceived by assisted reproduction and partly to higher rates of multiple pregnancies in assisted reproduction. In this study, we aimed to compare obstetric and perinatal outcomes of women conceived by *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) and spontaneously conceived pregnancies.

MATERIAL AND METHODS

This study was conducted in Ankara University, Department of Obstetrics and Gynecology in Turkey. Singleton pregnancies ended up with delivery after the 24th gestational weeks, between January 2006 and October 2012 were retrospectively screened. Necessary data were obtained from hospital records. One hundred and eighty singleton pregnancies were found to be conceived by *in vitro* fertilization/intracytoplasmic sperm injection within the selected study period and established as study group. The control group was established with randomly selected 624 women among spontaneously conceived singleton pregnancies that were delivered within the same period of time. Ethical approval for this study was obtained from Ethics Committee of Ankara University, Faculty of Medicine on November 10, 2014 (Approval number: 18-772-14).

The study and control groups were compared in terms of demographic characteristics, pregnancy complications such as gestational hypertension, preeclampsia, gestational diabetes mellitus, polyhydramnios, and oligohydramnios. Perinatal outcomes such as intrauterine growth retardation, preterm labor, LBW, neonatal intensive care unit administration, and APGAR scores were assessed as well.

In this study, pregnancy-induced hypertension was defined as new-onset increase in blood pressure after the 20th gestational week with a systolic blood pressure >140, diastolic blood pressure >90, and without proteinuria and without any new sign of end-organ dysfunction. Preeclampsia is defined as new-onset increase in blood pressure after the 20th gestational week with a systolic blood pressure >140, diastolic blood pressure >90 in the presence of proteinuria, or new sign of end-organ dysfunction. LBW is describes infants born <2500 g and preterm delivery was defined as deliveries occurred before the 37th gestational week. Polyhydramnios is defined as amniotic fluid index >24 cm and oligohydramnios is defined as amniotic fluid index <5 cm.

Table 1: Comparison of characteristics of IVF/ICSI and spontaneous conception groups

	IVF/ICSI	Spontaneous conception	p
Number	180	624	
Age (median)	29 (17–42)	28 (17–48)	**0.031**
Median maternal weight (kilogram)	60 (42–90)	63.5 (41–107)	**0.030**
Smokers	1.8%	1.9%	0.071
Maternal chronic diseases[a]	7.6%	7.5%	0.214

IVF/ICSI: *In vitro* fertilization/intracytoplasmic sperm injection; a: Chronic disease refers to chronic hypertension, thyroid dysfunctions, cardiopathies, rheumatologic conditions, chronic renal failures, and anemia.

One hour glucose tolerance test was performed for all women in the study population at the 24th gestational weeks for gestational diabetes screening. Women that serum glucose levels exceed 140 mg/dl were accepted positive and 3 h glucose tolerance test with 100 g glucose was applied for these women. Normal values for 100 g glucose tolerance test were accepted as lower levels than 95 mg/dL, 180 mg/dL, 155 mg/dL, and 140 mg/dL at the beginning of the test, 1st h, 2nd h, and 3rd h, respectively. Gestational diabetes was defined as new-onset diabetes in pregnancy and diagnosed with presence of at least two abnormal levels on 100 g oral glucose tolerance test.

Secondary sex ratio was defined as proportion of males in all live births.

All women included in this study have undergone a detailed obstetric ultrasonographic evaluation between the 18th and 22nd gestational weeks throughout their pregnancies. Detected fetal structural abnormalities in detailed obstetric ultrasonography were obtained from the records. Detailed obstetric ultrasonographic examinations were applied by three certified sonographers with Siemens Sonoline G50 ultrasound, Voluson E6, and Logiq 5P (GE medical systems) using 3, 5, and 5 MHz transducers.

Statistical analyses were performed with IBM SPSS Statistics 20.0 software. Categorical variables were expressed as number and percentages. Non-parametric data were compared by Mann–Whitney U-test and given as medians (interquartile range) or means (± standard deviations). P<0.05 was considered statistically significant.

RESULTS

A total of 804 singleton pregnancies that were end up with delivery after the 24th gestational weeks were evaluated in the study. One hundred and eighty (22.4%) of them were conceived by *in vitro* fertilization/intracytoplasmic sperm injection whereas 624 (77.6%) of them were conceived spontaneously.

Median ages of the study and control groups were estimated as 29 (17–42) and 28 (17–48). This difference was found statistically significant (p=0.031) (Table 1). Maternal weight of women with

Table 2: Comparison of obstetric and perinatal outcomes of IVF/ICSI and spontaneous conception groups

	IVF/ICSI	Spontaneous conception	p
Hypertensive disorders of pregnancy	10%	3.8%	**0.001**
Preeclampsia	5%	2.9%	0.161
Pregnancy-induced hypertension	5%	1%	**0.002**
Gestational diabetes mellitus	6.%	1.1%	**<0.001**
	Male factor infertility: 6.1%		**0.045**
	Other infertility etiologies: 8.6%		**0.008**
Cesarean rates	77.8%	51.7%	**<0.001**
Polyhydramnios	1.7%	1%	0.426
Oligohydramnios	3.9%	1.9%	0.157
Median gestational delivery week	37.2 (26.4–41.2)	38.7 (24.1–42.2)	**<0.001**
Median birthweight (g)	2800 (935–4560)	3230 (675–4970)	**<0.001**[a]
Total rate of low birth weight[b]	37.1%	7.2%	**<0.001**
Preterm delivery rate[c]	42.8%	11.5%	**<0.001**
Low birthweight in termly delivered infants[b]	8.7%	1.6%	**<0.001**
Apgar 1 min	7.42±1.83	8.18±1.31	**<0.001**
Apgar 5 min	8.69±227	9.33±1.19	**<0.001**
Neonatal intensive care unit administration[f]	27.2% (49)	7.05% (44)	**<0.001**
Length of neonatal intensive care (days)	7 (2–56)	6 (1–49)	0.146

IVF/ICSI: *In vitro* fertilization/intracytoplasmic sperm injection; a: After adjusting for maternal age and delivery week with covariance analysis, birth weights of spontaneous conception group and IVF/ICSI groups were found 3113.9±17.24 and 2999.0±33.43 g, respectively. Following this, adjustment differences in birth weights were found significant (p<0.001); b: Low birth weight was accepted as <2500 g; c: Preterm delivery refers to deliveries before the 37th week beginning from last menstruation; d: After adjusting for gestational week at delivery, no significant difference was found between two groups in terms of 1st min APGAR (p=0.213); e: After adjusting for gestational week at delivery, no significant difference was found between two groups in terms of 5th min APGAR (p=0.98); f: After adjusting for gestational week at delivery, no significant difference was found between two groups in terms of neonatal intensive care unit administration (p=0.161).

spontaneously conceived pregnancies was found significantly higher than women with IVF/ICSI pregnancies (p=0.030). Rate of maternal chronic diseases was found similar in the study and control groups (p=0.214) (Table 1). No differences were observed in terms of maternal smoking status among these two groups (p=0.071).

The overall rate of hypertensive complications of pregnancy (pregnancy-induced hypertension, preeclampsia, or eclampsia) was found 5.2% in whole study population. Hypertensive complications of pregnancy were found 10% of IVF/ICSI pregnancies and 3.2% of spontaneously conceived pregnancies (p=0.001). Pregnancy-induced hypertension rate was significantly higher in IVF/ICSI group in comparison to spontaneously conceived pregnancies (5% vs. 1%, respectively; p=0.002) whereas rates of preeclampsia were found similar between these two groups (5% vs. 2.9%, respectively; p=0.161) (Table 2).

In a second attempt to reveal whether the higher rate of hypertensive complications of pregnancy in IVF/ICSI pregnancies was dependent on a subgroup of women, we have divided IVF/ICSI pregnancies in two subgroups. These groups were as follows: IVF/ICSI pregnancies with hypertensive complications of pregnancies and IVF/ICSI patients without hypertensive complications in pregnancies. These two subgroups were compared in terms of maternal ages, basal FSH levels, basal estradiol (E2) levels, and administered total gonadotropin doses. However, neither of these parameters were found significantly different in this subgroup analysis (Table 3).

Total incidence of gestational diabetes mellitus was found 2.4% within the whole study population. Incidence of gestational diabetes mellitus was significantly higher in women conceived by IVF/ICSI in comparison with controls (6.7% vs. 1.1%, respectively; p<0.001). IVF/ICSI group was further subdivided into two subgroups in respect of infertility etiology. Subjects with male factor infertility and subjects with other infertility causes were considered as separate groups. Incidence of gestational diabetes mellitus was found 6.1% in subjects with male factor infertility and 8.6% in subjects with other infertility causes. Incidences of gestational diabetes mellitus were found significantly higher in these two subgroups in comparison with controls (p=0.045 and p=0.008, respectively). However, no significant differences were observed between these two subgroups in terms of gestational diabetes mellitus incidence (Table 2).

Median serum glucose concentration after 1 h glucose tolerance test was found as 110 (64–220) mg/dl in IVF/ICSI group and 109 (64–

Table 3: Comparison of women with and without hypertensive disorders of pregnancy among IVF/ICSI group

	Women with hypertensive disorders of pregnancy	Women without hypertensive disorders of pregnancy	p
Number	18	162	
Age (median)	28 (24–35)	29 (17–42)	0.921
Basal FSH value (mIU/mL)	6.79±2.60	6.63±2.53	0.696
Basal E2 value (pg/mL)	43.25±21.53	45.20 ±28.81	0.885
Total dose of gonadotropins (IU)	1819.33±1182.47	2269.26±966.78	0.563

IVF/ICSI: *In vitro* fertilization/intracytoplasmic sperm injection.

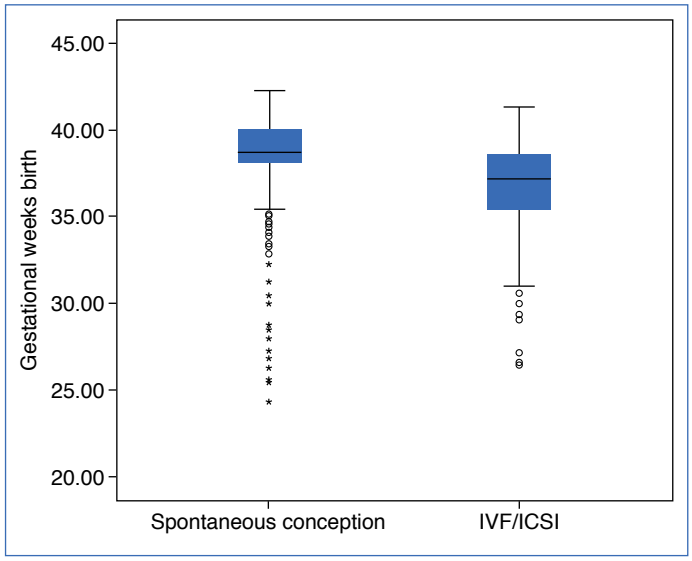

Figure 1: Comparison of gestational week at delivery between spontaneous conception and IVF/ICSI groups.

IVF/ICSI: *In vitro* fertilization/intracytoplasmic sperm injection.

220) mg/dL in spontaneously conceived pregnancies. This difference was found statistically significant (p=0.031). Diagnosis of gestational diabetes mellitus was established 42.9% of women whom glucose concentrations were higher than the previously mentioned cutoff level (≥140 mg/dL) in IVF/ICSI group. However, this rate was estimated as 28.3% in spontaneously conceived pregnancies. Furthermore, all of the women with a diagnosis of gestational diabetes mellitus in IVF/ICSI group were demonstrated to have ≥160 mg/dl serum glucose concentrations after 1 h glucose tolerance test.

In IVF/ICSI group, 77.8% of women were delivered by cesarean section whereas cesarean rate was 51.7% in spontaneous conception group. Cesarean rate in IVF/ICSI group was found significantly higher in IVF/ICSI group (p<0.001).

Oligohydramnios and polyhydramnios rates were found to be 3.9% and 1.7% in IVF/ICSI group and 1.9% and 1% in spontaneous conception group, respectively. No significant differences were found in terms of both parameters (p=0.157 and p=0.426, respectively).

Preterm delivery rate was 42.8% in IVF/ICSI group and this rate was significantly higher in comparison to spontaneously conceived pregnancies in which this rate was estimated as 11.7% (p<0.001). Gestational ages at delivery are shown in Figure 1. Median birth weight of IVF/ICSI group was 2800 (935–4560) g and 3230 (675–4970) g in spontaneous conception group. This difference was found statistically significant even after adjusted for gestational weeks at birth, maternal age, and maternal smoking status (p<0.001).

Infants with a birth weight below 2500 g were considered as LBW infants independent of the gestational weeks at birth. Significantly higher rate of LBW was found in IVF/ICSI pregnancies (37.1%) in comparison to spontaneously conceived pregnancies (7.2%) (p<0.001). Afterward, women delivered after the 37th gestational weeks were reevaluated considering the possible effects of higher preterm delivery rate in IVF/ICSI group on this great difference. Rate of infants with LBW was found as 8.7% in term delivered IVF/ICSI pregnancies and 1.6% in term delivered spontaneously conceived pregnancies. Rate of LBW infants was significantly higher in term delivered IVF/ICSI pregnancies (p<0.001).

Infants born in IVF/ICSI group showed significantly lower 1st and 5th min APGAR scores and showed significantly higher rate of neonatal intensive care unit administration (Table 2). However, considering the higher preterm deliveries in IVF/ICSI group, these results were adjusted for gestational weeks at delivery. After these adjustments, these differences have lost their statistical significance (Table 2). Median durations of hospitalizations at neonatal intensive care unit were similar in these two groups (p=0.146).

Incidences of abnormal detailed ultrasonography findings are summarized at Table 4.

Secondary sex ratios of these two groups were evaluated and male infant rate was found as 51.9% in spontaneously conceived pregnancies whereas it was found as 42.9% in IVF/ICSI pregnancies. This difference was found statistically significant (p=0.001). Secondary sex ratios were compared within the IVF/ICSI group in virtue of the infertility indication. Male born infant rate of subjects with male factor infertility in IVF/ICSI group was 40.8% and 46.1% in women with other causes of infertility. These two subgroups demonstrated a significant difference (p=0.002) (Fig. 2).

DISCUSSION

Birth weights of singleton infants conceived by assisted reproductive techniques have been shown to be reduced in comparison to spontaneously conceived pregnancies at the previous studies.[9] Results of our study supported by these previous findings. We have demonstrated that incidence of LBW infants was higher than spontaneously conceived pregnancies even after adjusted for maternal age and gestational weeks at birth. Moreover among term delivered infants, LBW was seen significantly higher in IVF/ICSI group. Exact reasons of these results are not clarified yet. Some of the studies demonstrated higher

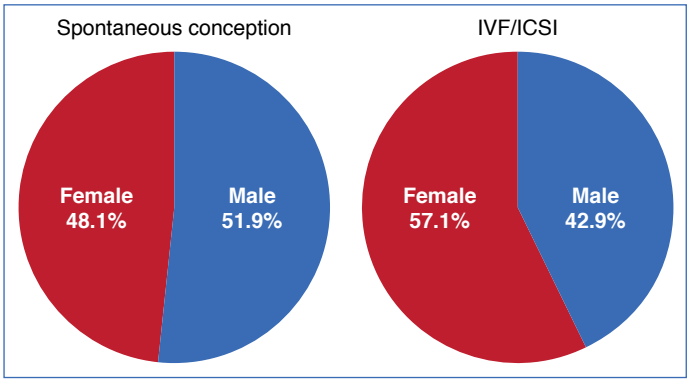

Figure 2: Distribution of infants due to gender in spontaneous conception and IVF/ICSI groups.

IVF/ICSI: *In vitro* fertilization/intracytoplasmic sperm injection.

placental microcalcification rates and more amount of villous edema.[10] Furthermore, a study conducted by Zhang et al.[11] who demonstrated a significant increase in blood-placenta barrier in women conceived by assisted reproduction. All these findings are expected to affect birth weight by a placental insufficiency phenomenon, however, the first trimester uterine artery pulsatility indexes were demonstrated to be similar in IVF and spontaneously conceived pregnancies.[12]

Causes of lower birth weights in IVF pregnancies may be depending on earlier phases of embryo development. A study conducted by Mercader et al.[13] who demonstrated increased mean birth weight in IVF pregnancies with cocultured embryos in comparison to conventionally cultured embryo transfers. Some growth factors such as IGF1, IGF2, VEGF, TGF, PAF, and EGF are secreted into the culture medium by auxiliary cells in coculture;[14] those might mimic the paracrine interaction between embryo and endometrial environment in spontaneous conception to some extent. Coculture procedure was not performed for any of subjects in our study population and lack of this early paracrine interactions might induce (or prevent) some epigenetic changes in embryos that might result with lower birth weights.

The previous studies demonstrated that preterm delivery rates in women conceived by assisted reproduction changes between 5.5% and 15% and these rates were 2 times higher in comparison with matched controls.[9] Thereby, these results in the literature indicate that a woman conceived by assisted reproduction carries a risk of preterm labor equivalent to a woman with history of one previous preterm delivery. In our study, IVF/ICSI pregnancies were shown to have a significantly higher risk of preterm delivery in comparison to spontaneously conceived women (p<0.001), likewise the other studies in literature. Neonatal intensive care unit administration rates of infants were found higher in IVF/ICSI group, however, the difference has lost its statistical significance after adjusted for gestational weeks at birth (p=0.161). Our results demonstrated that women conceived by IVF/ICSI should be handled with care during their pregnancy follow-ups in terms of preterm delivery nevertheless if the pregnancy was able to reach the term stage infant was not subjected to increased risk of neonatal intensive care requirement in comparison with spontaneous pregnancies.

There are many studies in literature that indicate an increased risk of preeclampsia and pregnancy-induced hypertension in women conceived by assisted reproduction.[15,16] These results were suggested to be associated with the differences in maternal ages that have not taken into account in some of the previous studies. However, a study conducted by Toshimitsu et al.[16] who demonstrated that pregnancy-induced hypertension rates were significantly higher in IVF/ICSI pregnancies independent of maternal ages. In our study, hypertensive complications of pregnancy were shown significantly higher in IVF/ICSI pregnancies (p=0.001). However, when we have separated the hypertensive complications of pregnancy into two subgroups as preeclampsia/eclampsia and pregnancy-induced hypertension, no significant difference was observed at rates of preeclampsia/eclampsia between IVF/ICSI pregnancies and spontaneous pregnancies. The rate of pregnancy-induced hypertension was significantly higher in IVF/ICSI group (p=0.002). Furthermore, mean maternal ages were found similar in women with and without hypertensive complications in pregnancy within IVF/ICSI group (p=0.921).

A study conducted by Woolringh et al.[17] who have shown an association between decreased ovarian reserve and hypertensive complications in pregnancy independent of maternal age in IVF/ICSI pregnancies. Woman with a decreased ovarian reserve could be expected to be a poor responder and may require higher doses of gonadotropins in ovulation induction. Thereby, total doses of gonadotropins required could be used as an indirect indicator of decreased ovarian reserve. In our study, median maternal ages, levels of pre-induction FSH, pre-induction E2, and total doses of gonadotropins required of women with and without hypertensive complications in pregnancy were compared within IVF/ICSI group. However, no significant differences were found in neither of these parameters (p=0.921; p=0.696; p=0.885; and p=0.563, respectively).

Although there are some studies with controversial results,[18] most of the studies indicate increased risk of gestational diabetes mellitus in both singleton and multiple pregnancies conceived by assisted reproduction.[19,20] Increased risk of gestational diabetes mellitus was suggested to be associated with factors such as etiology of infertility (PCOS and advanced maternal age), luteal phase support, effects of ovulation induction agents on maternal hormonal milieu, or exacerbation of underlying maternal metabolic and vascular factors by *in vitro* fertilization therapy. A study conducted by Ashrafi et al.[21] who demonstrated an association between increased rates of gestational diabetes mellitus and luteal phase support proceeding beyond the 12th gestational weeks in pregnancies conceived by assisted reproduction. In our study, rate of gestational diabetes was found significantly higher in IVF/ICSI pregnancies in comparison with spontaneous pregnancies (p<0.001). Routine clinical practice adopted in our institution includes cessation of luteal phase support at the 12th gestational weeks so luteal phase support was unlikely to be the cause of our results.

Factors that could be related with subfertility such as polycystic ovary syndrome and advanced maternal age were known to be associated with increased risk of GDM. In our study, we have reevaluated the incidence of GDM due to etiology of infertility. We have separated the IVF/ICSI group into two subgroups due to etiology of infertility as male factor infertility and other infertility causes. Incidences of GDM were found significantly higher in both subgroups in comparison with spontaneously conceived pregnancies, however, no significant differences were observed between these two subgroups.

Results of 50 g glucose tolerance tests were also evaluated in our study. Among women with ≥140 mg/dL results, 42.9% were found to be diagnosed as GDM in IVF/ICSI group and serum glucose concentrations of all women with a diagnosis of GDM in IVF/ICSI group were observed to be ≥160 mg/dL. Although the limited study population obviates us to reach a clear threshold level in 50 g glucose tolerance test for IVF/ICSI pregnancies, adopting higher threshold levels in 50 g glucose tolerance test for IVF/ICSI pregnancies may decrease the false positivity rates for women conceived by IVF/ICSI. Further studies with larger sample sizes are needed in this aspect.

CONCLUSION

Singleton pregnancies conceived by IVF/ICSI propose higher risk in terms of some adverse perinatal outcomes comparing to spontaneously conceived singleton pregnancies. Obstetricians should be aware of some possible complications in follow-ups of these pregnancies. Higher incidences of LBW infants, preterm deliveries, and associated admission to neonatal intensive care unit besides the risk of developing gestational diabetes mellitus warrant close monitoring and careful management in these pregnancies.

Statement

Ethics Committee Approval: The Ankara University Clinical Research Ethics Committee granted approval for this study (date: 10.11.2014, number: 18-772-14).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – BB; Design – AK; Supervision – FT; Resource – AK; Materials – AK; Data Collection and/or Processing – AK; Analysis and/or Interpretation – AK; Literature Search – FT; Writing – AK; Critical Reviews – BB.

Conflict of Interest: The authors have no conflict of interest to declare.

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