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Original Article

## Ivf versus spontan singleton pregnancies fetal and maternal outcomes in a tertiary care hospital

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### ABSTRACT:

**Background:** We aimed to compare perinatal outcomes of intracytoplasmic sperm injection (ICSI) versus naturally (spontaneously) conceived age and parity matched group of singleton pregnancies.

**Methods:** Two hundred and sixteen singleton pregnancies aged between 18-45 years old were included in this study. Among all study group, 106 cases were ICSI pregnancies (study group) and 110 cases were spontaneously conceived singleton pregnancies (control group). Pregnancy outcome parameters were: the incidence of chronic hypertension, preeclampsia, gestational hypertension, placenta previa, placental abruption, preterm birth, intrahepatic cholestasis of pregnancy, gestational diabetes, preterm premature rupture of membranes, caesarean delivery.

**Results:** There were no differences in terms of maternal age, BMI, gravidity, parity, gestational weeks at birth and birth weight between ICSI and spontaneously conceived pregnancy groups. Placental abruption, gestational diabetes and cesarean section rates were significantly higher in ICSI pregnancies than spontaneously conceived pregnancies (4.7% vs 0%, 21.7% vs 11.8% and 82.1% vs 68.2%, respectively). There were no statistically significant differences in terms of chronic hypertension, preeclampsia, gestational hypertension, preterm labor, placenta previa, intrahepatic cholestasis of pregnancy, preterm and term premature rupture of the membranes.

**Conclusion:** ICSI pregnancies have higher adverse perinatal outcomes than spontaneously conceived singleton pregnancies which were matched with age and parity. That's why ICSI pregnancies should be given a detailed counseling about the adverse perinatal outcomes and should be followed up more carefully through the pregnancy.

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**Key words:** ICSI; singleton pregnancy; perinatal outcome

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### Introduction

First invitro fertilization (IVF) baby, Louise Brown was born in 1978 in the United Kingdom[1]. After than, first ICSI procedure was performed successfully in 1992. Especially it was a great chance for male infertility who had severe sperm defects [2]. So this method was hopeful for the couples who were unsuccessful with conventional IVF methods.

Although there are many pregnancies born with healthy outcomes in ART cycles, there are also many reports on increased risks of maternal, fetal and neonatal outcomes (such as preeclampsia, placenta previa, gestational diabetes, preterm labor, premature rupture of membranes, ablation placenta, low birth weight etc.) in IVF pregnancies compared to the naturally conceived pregnancies [3-6]. Although, the majority of the adverse outcomes related to the multiple pregnancies[7], singleton pregnancies with IVF cycles have also increased

obstetrical and neonatal risks compared to the naturally conceived singleton pregnancies. Micromanipulations in oocytes, sperms and zygotes, medications and culture systems used maybe the cause of abnormal implantation in endometrium and cause these adverse outcomes.

We aimed to compare the obstetric and neonatal outcome parameters of singleton ICSI pregnancies with naturally conceived singleton pregnancies in ART department of our tertiary obstetric clinic.

### Material-Methods

This retrospective study was conducted between February 2012 and April 2013 in Obstetric Department of Zeynep Kamil Women and Children Diseases Training and Research Hospital in Istanbul. The pregnancies leading to a live birth

(>28 weeks gestation or >1200 g birth weight) were included in this retrospective cohort study. A total of 216 singleton pregnant women ages between 18-45 years old were included in this study, there were 106 cases who conceived by ICSI(study group) while 110 cases conceived spontaneously(control group). Groups were matched in terms of age and parity.

Maternal demographic parameters such as age, body mass index (BMI), gravidity, parity, gestational age at birth; obstetric complications such as preeclampsia(blood pressure >140-90 mm-Hg and proteinuria>300mg/day after 20 weeks gestation), gestational hypertension (blood pressure >140-90 mmHg without proteinuria onset during gestation), chronic hypertension (blood pressure>140-90mmHg before gestation), gestational diabetes (diagnosed after 100 gr glucose loading test according to Carpenter-Couston criteria), placental previa and placental abruption, hepatic cholestasis, preterm membrane rupture(rupture of membranes after 37 weeks of gestation before contractions), premature preterm membrane rupture(rupture of membranes before 37 weeks gestation), mode of delivery, birth weight and fetal complications such as neonatal intensive care unit (NICU) stay, respiratory distress syndrome and hospital stay more than 10 days were all recorded.

Data were obtained from maternal and neonatal delivery and hospitalization records. Ethics committee approval was obtained from Zeynep Kamil Women and Children Diseases Training and Research Hospital Ethics Committee. (Date and number 23<sup>rd</sup> of may 2014- 76)

**Statistical analyses**

Statistical analyses were performed using SPSS software program. Demographic characteristics were presented as mean ±standard deviations or frequencies or percentages. Comparisons between ICSI and spontaneous singleton pregnancies variables for maternal and fetal results t-tests (Wilcoxon-tests) or chi<sup>2</sup>-tests (Fisher’s exact tests) were used. P-values <0.05 were considered statistically significant.

**Results**

The maternal and fetal demographic characteristics in both groups were shown in Table 1.

**Table 1 Demographic characteristics.**

	ICSI pregnancies mean (standart deviation)	Spontaneous pregnancies mean (standart deviation)	P value
Age (year)	32.37±4.80	32.36±4.88	p>0.05
BMI (kg/m2)	26.23±4.77	30.02±2.85	p>0.05
Gravida	1.29±0.57	1.25±0.49	p>0.05
Parity	0.17±0.44	0.15±0.40	p>0.05

Gestational weeks at birth (days)	258.5±23.07	259.9±23.46	p>0.05
Birth weight (gram)	2863.86±770.42	2797.48±770.19	p>0.05

There were no differences between ICSI and spontaneously conceived pregnancies in terms of maternal age, BMI, gravidity, parity, gestational weeks at birth and birth weight.

Obstetric outcomes were shown in Table 2.

**Table 2: Obstetric outcomes.**

	ICSI pregnancies N=number (%)	Spontaneous pregnancy N=number (%)	P value
Chronic hypertension	3 (2.8)	2 (1.8)	P>0.05
Preeclampsia	14 (13.2)	18 (16.6)	p>0.05
Gestational hypertension	10 (9.5)	4 (3.6)	p>0.05
Preterm labor	19 (18.1)	11 (10.0)	p>0.05
Ablatio placenta	5 (4.7)	0 (0)	<b>P&lt;0.05</b>
Placenta previa	5 (4.7)	1(0.9)	p>0.05
Intrahepatic cholestasis of pregnancy	4 (3.8)	3 (2.7)	p>0.05
Gestational diabetes	22 (21.7)	13 (11.8)	<b>P&lt;0.05</b>
Preterm premature rupture of membranes	7 (6.6)	4 (3.6)	p>0.05
Preterm rupture of membranes	7 (6.6)	9 (8.2)	p>0.05
Cesarean section	87 (82.1)	75 (68.2)	<b>P&lt;0.05</b>

Placental abruption, gestational diabetes and cesarean section rates were statistically higher in ICSI pregnancies than spontaneously conceived pregnancies (4.7% vs 0%; 21.7% vs 11.8% and 82.1% vs 68.2%). There were no statistically significant differences in the rates chronic hypertension, preeclampsia, gestational hypertension, preterm labor, placenta previa, intrahepatic cholestasis of pregnancy, preterm and term premature rupture of the membranes.

Neonatal outcomes were shown in table 3.

**Table 3: Neonatal outcomes**

	ICSI pregnancies N=number (%)	Spontaneous pregnancies N=number (%)	P value
Respiratuar distress syndrome	19 (18.3)	20 (18.3)	p>0.05
NICU admission	28 (26.4)	39 (35.5)	p>0.05
Hospitalisation longer than 10 days	2 (1.9)	7 (6.4)	p>0.05

There were no statistically significant differences in terms of the rates of neonatal respiratory distress syndrome, NICU admission and neonatal hospitalization days longer than 10 days between the two groups.

### Discussion

There are many reports in the literature that IVF pregnancies have higher adverse pregnancy outcomes, but most of them did not studied only singleton pregnancies and none of them reported maternal age adjusted complication rates [8,9]. We know that the incidence of adverse obstetric outcomes such as preeclampsia, gestational diabetes, placental abruption, placenta previa and abnormal labor have been observed with a higher rate in women with advanced ages [10,11]. That's why we have chosen maternal age and parity matched singleton pregnancies in control group.

We found higher rates of ablatio placenta, gestational diabetes and cesarean section rates in ICSI pregnancies than spontaneously conceived pregnancies.

Suzuki et al. [12] concluded that in elderly pregnant patients (age>35 years) cesarean rates were higher in IVF pregnancies than spontaneously conceived pregnancies but they found no statistical difference between other obstetric outcomes between the groups. Also Suzuki et al., stated that placental abruption in over 35 years old patients conceived by IVF was observed with four fold increased rate compared to spontaneously conceived 20-29 years old patients. However, the differences were not statistically significant in both elderly (over 35 years old patients) IVF and spontaneously conceived groups. In our study, we selected matched age control groups, and found higher placental abruption rates in ICSI group of patients than spontaneously conceived patients. Suzuki et al. [13] also studied obstetric outcomes of IVF patients over 35 years old and below 35 years old IVF patients. They found no difference in means of placental abnormality, premature delivery or neonatal asphyxia between the two groups. Hence they concluded that obstetric complications in pregnancies conceived by IVF are attributed to mechanisms other than those that depend on advanced maternal age.

Dayan et al. [14] compared IVF and ICSI singleton pregnancies with spontaneously conceived pregnancies in a

population based study, and concluded that the rate of chronic hypertension and gestational diabetes rates were statistically higher in ART pregnancies than spontaneously conceived pregnancies. They also concluded in the same study that, increased placental complications were accompanied with hypertension. In our study we found similar the rates of chronic hypertension, gestational hypertension and preeclampsia between ICSI and spontaneously conceived pregnancies. But we also found statistically significantly higher rates of placental abruption. So In contrast to Dayan hypothesis, we believe, ART was an independent risk factor for placental complications.

Egbe et al. [15] showed higher cesarean rates in IVF pregnancies than the naturally conceived ones (4.1 times more), which supports our results. They included 102 cases (51 IVF and 51 control cases), in their study, both singleton and multiple pregnancies were included. They did not evaluate placental abruption, gestational diabetes and they did not find any significant difference between the groups in terms of birth weight, gestational age at delivery and Apgar scores of neonates. As the maternal and fetal complications were high in multiple pregnancies, we only included singleton pregnancies.

Cesarean section rates were so high in our study in both groups. Because our hospital is tertiary referral hospital and majority of the cases are high risk pregnancies. In our study, history of previous cesarean rates were also disregarded. Increased cesarean rates in study group were mainly due to high anxiety levels of both patients and obstetricians about adverse outcomes of fetus and the mother. Also increased gestational diabetes rates which resulted in increased cesarean rates.

Nouri et al. [16] studied obstetric and perinatal outcomes in IVF versus ICSI-conceived pregnancies and they concluded that the birth weight and 1 and 10 minute Apgar scores were lower in ICSI group than IVF group and ICSI-conceived children were more often hospitalized at a neonatal intensive care unit than IVF children. All our cases were ICSI patients so if we had used IVF procedure instead of ICSI, the adverse outcomes would have decreased or disappeared.

Dhont et al. [17] studied perinatal outcome of IVF and ICSI pregnancies in case control study. They found no differences in perinatal outcomes (birth weight, perinatal mortality, mean hospital stay, NICU admission) in ART singleton pregnancies than age, parity matched singleton controls. But ART cases were either IVF or ICSI, they did not compare each group with control groups.

Jackson et al [18], reported a meta-analysis about perinatal outcomes in singletons following in vitro fertilization. Fifteen studies comprising 12,283 IVF and 1.9 million spontaneously conceived singletons were included in that meta-analysis. They found that compared with spontaneous conceptions, IVF singleton pregnancies were associated with significantly higher odds ratios: perinatal mortality (odds ratio [OR] 2.2; 95% confidence interval [CI] 1.6, 3.0), preterm delivery (OR 2.0; 95% CI 1.7, 2.2), low birth weight (OR 1.8; 95% CI 1.4,

2.2), very low birth weight (OR 2.7; 95% CI 2.3, 3.1), and small for gestational age (OR 1.6; 95% CI 1.3, 2.0). Early preterm delivery, spontaneous preterm delivery, placenta previa, gestational diabetes, preeclampsia, and neonatal intensive care admission were also significantly more prevalent in the IVF group. So, they concluded that IVF patients should be informed of the increased risk for adverse perinatal outcomes.

Allen et al [19], reported that singleton ART pregnancies have an increased risk of preterm delivery and low birth weight at term. Non-lethal congenital malformation rates are not increased following ART. Placenta previa was increased following ART. We found no difference in means of placenta previa, preterm delivery and low birth weight rates in our study.

Tsutsumi et al.[20] studied singleton pregnancy outcomes after assisted and non-assisted reproductive technology in infertile patients. They studied Pregnancy outcome parameters such as pregnancy induced hypertension, placenta previa, placental abruption, cesarean delivery, preterm birth, very preterm birth, stillbirth, low birth weight and very low birth weight. They concluded that only ART procedure may be a risk factor for the development of placenta previa. Other abnormal perinatal outcomes that had been previously attributed to ART, may be due to the baseline characteristics of infertile patients.

In a systematic review [21], Shevell et al. [3] found that increased maternal complications such as 6 fold high increased placenta previa, 1.6 fold high gestational hypertension, 0.5 fold higher gestational diabetes, 2.4 fold high placental abruption, 2 fold higher caesarean delivery rates. Kallen et al. [22] and Romundstad et al. [23] found increased placenta previa rates in IVF cycles than naturally conceived pregnancies, 4 fold and 6 fold higher respectively. Allen et al. [24] also emphasized increased maternal complications in IVF pregnancies, 2 fold higher in gestational hypertension, gestational diabetes and caesarean deliveries than naturally conceived singleton pregnancies. We only found higher rates of gestational diabetes, placental abruption and caesarean rates in our study. We did not find any difference in terms of placenta previa rates.

As in our study, Silberstein et al. [25] (in a large population based study, IVF; n=1296 and singleton pregnancies conceived spontaneously, n=172 288) pointed out increased gestational diabetes risk in IVF pregnancies than conceived spontaneously (OR=1.77, 95% CI:1.52–2.07, p<0.001).

Limitations : As we included the patients from delivery (maternity) hall in our hospital we couldn't compare the congenital anomaly rates including aneuploidies and epigenetic or imprinting disorders and major birth defects in both groups and the sample size were small for both the study and control groups. Long-term outcomes such as neuro-developmental or neuro-behavioral development of the child in ART pregnancies were not studied.

## Conclusion

As the pregnancies achieved by ICSI have higher adverse perinatal outcomes; closer follow-up should be done and careful counseling should be offered to this pregnant population. Detailed studies, done with fresh or frozen embryos, IVF or ICSI procedures and embryo transfer at 3<sup>rd</sup> or 5<sup>th</sup> day of embryo may have different perinatal outcomes.

## Conflict of interest

The authors report no conflict of interest

## Founding source

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