

ART AND PERINATAL OUTCOMES OBSTETRIC AND PERINATAL OUTCOMES, AMONG COUPLES WITH MALE FACTOR INFERTILITY, AFTER ASSISTED CONCEPTION: A MATCHED CASE-CONTROL STUDY

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SUMMARY

Objective: Present study was designed to evaluate the possible differences in obstetric and perinatal outcomes of the male factor infertility subgroup, following assisted reproduction.

Design: A matched case-control study was performed on obstetric and perinatal outcomes of pregnancies following ART with male factor infertility diagnosis.

Setting: The IVF center of one university (Gazi University School of Medicine) and one private hospital (Guven) and their obstetric departments in Ankara, Turkey, participated in the study.

Patients: Study group was confined to 97 pregnancies following ART with male factor infertility diagnosis (146 neonates). Two separate control groups were chosen; one from spontaneously conceived pregnancies (207 pregnancies and 250 neonates), and other from pregnancies following ART with all other causes of infertility (108 pregnancies and 145 neonates), matched according to numerous parameters that may influence pregnancy outcomes (e.g. number of children at birth, maternal age, parity, etc).

Main outcome measures: Maternal complications, birth weight, duration of gestation, perinatal morbidity and mortality, incidence, indication and duration of neonatal hospitalization and incidence of congenital malformations.

Results: Lower birth weight and shorter duration of gestation were observed among singletons of the male factor infertility subgroup compared to natural conception singletons. Nevertheless, adjusted analyses considering length of the duration revealed no differences.

Conclusions: For the couples with male factor infertility conceived with ART, the overall obstetric and perinatal outcomes were similar with other infertility subgroups and spontaneously conceived ones.

Key words: assisted reproductive technologies, male factor infertility, perinatal outcomes

ÖZET

Erkek Faktör İnfertilitesi Tanısı olan Çiftlerde, Yardımla Üreme Sonrası, Obstetrik ve Perinatal Sonuçlar: Eşleştirilmiş Vaka-Kontrollü Çalışma

Objektif: Sunulan çalışmada, erkek faktör tanısı olan infertil grupta, Yardımla Üreme Teknikleri sonrası obstetrik ve perinatal sonuçlar değerlendirilmiştir.

Planlama: Yardımla Üreme Teknikleri sonrası obstetrik ve perinatal sonuçları karşılaştırmak üzere, eşleştirilmiş vaka-kontrol çalışması olarak planlanmıştır.

Ortam: Ankara'da bir üniversite (Gazi Üniversitesi, Tıp Fakültesi) ve bir özel hastanenin (Güven Hastanesi) IVF üniteleri ve obstetri bölümleri çalışmaya alınmıştır.

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Art and perinatal outcomes obstetric and perinatal outcomes, among couples with male factor infertility, after assisted conception

Hastalar: Erkek faktör tanısı olan infertil gruptaki ,Yardımla Üreme Teknikleri sonrası 97 gebelik ve 146 yenidoğan, çalışma grubu olarak alınmıştır. Biri spontan gebelik (207 gebelik, 250 yenidoğan), biri de, diğer faktörler nedeni ile infertil olan gruptan oluşan (108 gebelik, 145 yenidoğan) iki ayrı kontrol grubu oluşturulmuş ve gebelik sonuçlarını etkileyebilecek birçok parametre yönünden eşleştirilmiştir. (fetus sayısı, maternal yaş, parite vs.)

Değerlendirme parametreleri: Maternal komplikasyonlar, doğum ağırlığı, gebelik süresi, perinatal morbidite ve mortalite, neonatal hospitalizasyonun insidans, endikasyon ve süresi ve konjenital malformasyon insidansı.

Sonuç: Spontan tekil gebeliklerle karşılaştırıldığında, erkek faktörü infertilite grubunun tekil gebeliklerinde, daha düşük doğum ağırlığı ve gebelik süresi izlendi. Ancak analizler gebelik süresine göre tekrar düzenlendiğinde, bu fark ortadan kalktı.

Yorum: Spontan gebelikler ve diğer infertilite gruplarıyla karşılaştırıldığında, erkek faktör infertilitesi nedeniyle yapılan Yardımla Üreme Teknikleri gebelikleri için, obstetrik ve perinatal sonuçlarda bir fark izlenmedi.

Anahtar kelimeler: erkek faktör infertilitesi, perinatal sonuçlar, yardımla üreme teknikleri

BACKGROUND

Since the birth of the first in vitro fertilization (IVF) baby more than 25 years ago, Assisted Reproductive Technologies (ART) have evolved constantly. Various techniques have been developed some of which were quite invasive, such as, intracytoplasmic sperm injection (ICSI) with mature and immature sperm cells, embryo biopsy for preimplantation genetic diagnosis (PGD) and ooplasmic transfer. ART have been blamed with various obstetric and perinatal complications because of the micromanipulation of the early embryo, artificial microenvironment, as well as the use of immature sperm cells. Retrospective and prospective follow-up studies from different centers have raised great concern by suggesting that pregnancies achieved by ART were subject to major complications such as increased risk of low birth weight (LBW), and perinatal mortality, mainly because of prematurity, even after adjusting for age, parity, and multiplicity.

Recently, Schieve. et al. concluded that, singletons born after ART remain at increased risk for adverse perinatal outcomes; however, risk for term LBW declined from 1996 to 2000, whereas preterm LBW was stable⁽¹⁾. Furthermore, there is inconclusive evidence that ART may be associated with genetic imprinting disorders. For childhood cancer, chronic conditions, learning and behavioral disorders, and reproductive effects there is insufficient empirical research to date, but given the data for more proximal outcomes, these outcomes merit further study⁽²⁾. While IVF has always been considered as a relatively safe procedure, ICSI has raised immediate concerns about its potential risks related to micromanipulation

procedure⁽³⁾. In addition to ART, increased obstetric and perinatal risks that have been suggested by some studies may be attributed to the infertility itself. Only a few studies have addressed the possible differences in pregnancy outcomes in different infertility subgroups^(4, 5). The aim of the present study was to compare the obstetric and perinatal outcomes of couples who had male factor infertility diagnosis and had babies after IVF or ICSI with those of matched controls of the other infertility subgroups and spontaneously conceived pregnancies. By emphasizing on the male factor, we excluded the effect of female infertility status and possible adverse in-vivo environment for embryo development.

The study revealed solely the effect of the ART treatment with paternal contribution.

MATERIAL AND METHODS

Selection of Participants

The IVF center of one university (Gazi University School of Medicine) and one private hospital (Güven) and their obstetric departments in Ankara, Turkey, participated in the study. Pregnancies following ART with male factor infertility diagnosis were defined as the study group. WHO criteria were used for the diagnosis of male factor infertility (6). Two separate control groups were chosen from the registry of same hospitals. Control group I was spontaneously conceived pregnancies and Control group II was pregnancies following ART with other infertility diagnosis, such as tuboperitoneal factor, anovulation, and unexplained infertility. Pregnancies following ART with more than

a single indication were excluded. Control pregnancies were selected if the following criteria were met; maternal age no more than 2 years apart from that of the case, same parity, same ethnicity, the date of parturition no more than 2 years apart from that of case, comparable height (+10 cm) and weight (+10 kg), same smoking habits, same obstetric and medical history for factors that may effect the outcomes of a subsequent pregnancy. The spontaneously conceived pregnancies had to be achieved without any kind of infertility treatment; in addition, the obstetric care had to be provided by the same clinic that provided the obstetric care for ART pregnancies. Most patients also gave birth in these centers (96.5%). We excluded ART pregnancies, which were achieved by transfer of frozen embryos and in which embryo reduction was performed. Technical Information

Throughout the study period, the treatment protocols remained generally stable. The standardized ovarian stimulation protocol for ART was used in all IVF (3%) and ICSI (97%) cycles. Pituitary down-regulation with a gonadotrophin releasing hormone analogue (GnRHa), was followed by daily injections of gonadotrophins. Oocyte retrieval was performed, 35- 36 hours after administration of human chorionic gonadotropin (hCG), by ultrasound-guided transvaginal aspiration. Embryo transfer (ET) was performed 2 to 5 (mostly 3) days after follicle aspiration. The luteal phase was supplemented with vaginally administered progesterone. Procedures involving ART were defined as procedures for the treatment of infertility in which both oocytes and sperms were handled outside the body; these include IVF and ICSI with transcervical ET. Gestational age at delivery in ART pregnancies was defined as the time between the date of ET and the date of delivery plus 14 days whereas in spontaneously conceived pregnancies, it was defined as the number of days between the date of delivery and the date of the first day of the last menstrual period. In the analysis, we included only pregnancies leading to births >20 weeks' gestation or >500 gram (g) birth weight. We defined LBW as 2500 g or less and very LBW as less than 1500 g. Preterm delivery for singletons was defined as a delivery before 37 completed weeks. Although prematurity was not certainly defined for twins, we used 36 completed weeks. A caesarean section was called elective if performed before the onset of labor without any obstetrical indications. A major congenital

anomaly was defined as a significant congenital structural malformation or chromosomal defect. A smoker was defined as a woman who smoked at least during the first trimester of her pregnancy.

Statistical Analysis

The records of the participants were reviewed and the data, which were obtained from the IVF unit files, antenatal care records, maternal and neonatal delivery, and hospitalization chart, were collected on standard forms. The recorded details included medical and obstetric history, evaluation, and cause of infertility, the ART cycle that led to the conception, pregnancy course and any antenatal complications and admissions to the neonatal intensive care unit.

The main outcome measures were, duration of gestation, birth weight, perinatal morbidity, and mortality and the incidence of congenital malformations, with the incidence, indication and duration of neonatal hospitalization. Complicated pregnancies with gestational hypertension, gestational diabetes mellitus, intrauterine growth restriction, amnion fluid disorders, and placental disorders were considered as maternal adverse outcomes. Analyses were conducted separately for singletons and twins. The triplets were excluded from the subgroup analysis as birth-number group; because matching controls were insufficient for them in the same centers' birth registries (16 vs. 2 triplets). In addition, we subdivided birth weight outcomes into term and preterm infants. Within each birth-number group, we examined the risk of low and very low birth weight. SPSS (Ver.11.0 Inc Chicago IL-USA) was used for the data analysis of the study. Comparisons between groups and statistical analysis were performed by using independent samples T and Chi-Square tests. Statistical significance was defined as $P < 0.05$.

RESULTS

In the present analysis, we included the pregnancies conceived through ART procedures that were performed in Gazi University School of Medicine, Department of Obstetrics and Gynecology, Reproductive Endocrinology, and Infertility Section with Guven Hospital Assisted Reproductive Technologies Center, IVF Unit, between 1999-2004. Of 676 IVF, completed oocyte pick-up and ET procedures, 50% resulted in

clinical pregnancy. Of these pregnancies, 225(67%) proceeded to delivery of one or more live born infants, the remaining 113(33%) resulted in spontaneous abortion. ART indications were various [tuboperitoneal factor (12.7%), male factor (42.8%), anovulation (12.2%), and unexplained infertility (25.4%)] and 6.9% had more than a single indication.

Because some of these were multiple-birth deliveries, the total number of infants was 146, following ART with male factor infertility diagnosis with 250 and 145 infants for control group I and II, respectively. A total of 13 pregnancies and 17 infants with missing data on maternal and perinatal outcomes were also excluded.

Maternal Characteristics

Maternal age, parity, and origin were similar in all

groups. All of our cases were Caucasian women. Considering maternal medical illness, there was one patient with chronic hypertension in the study group and three in the control groups. There were two patients with overt diabetes mellitus in the study group and two in the control groups. In addition to the matched criteria, there were no significant differences in the outcome of previous pregnancies. Two smokers in the study and three in the control groups were comparable. All patients in the study and control groups underwent elective or emergent cesarean sections. (Tables I and II). Pregnancies following ART with male factor infertility diagnosis versus spontaneously conceived pregnancies Ninety-seven pregnancies following ART with male factor infertility diagnosis were included. There were 58 singletons (59.7%), 29 twins (29.9%),

Table I: Maternal characteristics of singleton pregnancies

	STUDY GROUP (S) (n=58)	CONTROL GROUPS		P	
		(I) (n=166)	(II) (n=77)	(S vs I)	(S vs II)
Mean Maternal Age ± SD	31.5±3.6	30.5±3.3	32.1±2.4	NS	NS
Mean Parity ± SD	0.4±0.2	0.5±0.1	0.4±0.3	NS	NS
Height (cm) ± SD	162±13.5	163±22.5	161±21.7	NS	NS
Weight (kg) ± SD	66±11.7	68±21.9	67±17.7	NS	NS
Obstetric history* (%)	7 (12.0)	19 (11.4)	10 (12.9)	NS	NS
Obstetric department** (%)	55 (94.8)	162 (97.5)	73 (94.8)	NS	NS

(S). Pregnancies following ART with male factor infertility diagnosis (I). Spontaneously conceived pregnancies (II). Pregnancies following ART with other infertility diagnosis

NS: No significance *Percentage of women with previous miscarriage, termination of pregnancy, ectopic pregnancy, or stillbirth **Percentage of women whose antenatal care have been provided by the same obstetric department

Table II: Maternal characteristics of twin pregnancies

	STUDY GROUP (S) (n=29)	CONTROL GROUPS		P	
		(I) (n=39)	(II) (n=25)	(S vs I)	(S vs II)
Mean Maternal Age ± SD	32.4±4.5	31.7±3.1	31.6±3.2	NS	NS
Mean Parity ± SD	0.3±0.1	0.4±0.2	0.2±0.2	NS	NS
Height (cm) ± SD	166±12.5	164±31.3	163±13.5	NS	NS
Weight (kg) ± SD	64.8±16.5	65±17.9	63±21.4	NS	NS
Obstetric history* (%)	2 (6.8)	3 (7.7)	2 (8.0)	NS	NS
Obstetric department* (%)	28 (96.5)	39 (100)	23 (92.0)	NS	NS

(S). Pregnancies following ART with male factor infertility diagnosis (I). Spontaneously conceived pregnancies (II). Pregnancies following ART with other infertility diagnosis NS: No significance *Percentage of women with previous miscarriage, termination of pregnancy, ectopic pregnancy, or stillbirth

**Percentage of women whose antenatal care have been provided by the same obstetric department

and 10 triplets (10.3%), with 146 neonates. Two hundred seven pregnancies [166 singletons (81%), 39 twins (18.8%), and 2 triplets (0.96%)] were included in the control group I.

Singleton infants of the study group carried on increased risk for LBW compared to singletons of the control group I. Furthermore, singletons of the study group tended to be born earlier than singletons of the control group I. We therefore further adjusted our analysis according to whether they were born at term or preterm. This adjustment significantly changed our findings, and we did not find the same difference. Birth weights of the singleton infants of the study group at term was similar with singletons of the control group I. In addition, their birth weights were not lower than control group I at preterm (Table III). We observed no excess risk of low birth weight among the singletons conceived

with ART who were born at any week of gestation between 37 and 41 weeks. For twins of the study group, both term and preterm birth weights were similar to control group I. (Table IV).

There were no statistically significant differences in the rates of gestational diabetes mellitus (P: 0.42 for singletons, P: 0.72 for twins) and gestational hypertension (P:0.97 for singletons, P: 0.67 for twins) between the study group and control group I. Placental pathologies, amnion fluid disorders, and intrauterine growth restrictions were observed in only few cases; therefore, they were not analyzed in subgroups. The neonatal outcomes of the study group did not differ significantly from that of control group I. There were no significant differences in the incidence, and indication of the neonatal intensive care unit hospitalization. The duration of the neonatal

Table III: Gestational duration and birth weights of singleton pregnancies

	STUDY GROUP (S) (n*=58)	CONTROL GROUPS		P	
		(I) (n*=166)	(II) (n*=77)	(S vs I)	(S vs II)
Gestational age at birth (weeks) ± SD	37.5±12.4	38.3±15.7	37.4±13.8	0.02†	NS
Birth weight (g) ± SD	3146.21±316.29	3354.42±624.12	3124.51±451.76	0.03††	NS
Birth weight (g) ± SD (>37 weeks)	3210.24±421.32	3388.49±365.53	3198.43±615.43	NS	NS
Birth weight (g) ± SD (>37 weeks)	3056.44±354.54	3105.73±418.22	3102.57±356.43	NS	NS
Low birth weight (<2500g) (%)	3 (5.2)	2 (1.2)	3 (3.9)	NS	NS
Very low birth weight (<1500g) (%)	2 (3.4)	1 (0.6)	1 (1.3)	NS	NS

(S). Pregnancies following ART with male factor infertility diagnosis (I). Spontaneously conceived pregnancies (II). Pregnancies following ART with other infertility diagnosis NS: No significance *n=Number of neonates † CI: 0.62 [0.37-0.95] †† CI: 0.54 [0.42-0.68]

Table IV: Gestational duration and birth weights of twin pregnancies

	STUDY GROUP (S) (n*=58)	(I) (n*=78)	(II) (n*=50)	P	
				(S vs I)	(S vs II)
Gestational age at birth (weeks)±SD	35.7±12.4	35.2±11.6	35.4±11.2	NS	NS
Birth weight (g) ±SD	3026.63±218.11	3063.65±624.12	3098.53±451.76	NS	NS
Birth weight (g) ±SD (>37 weeks)	3073.42±240.37	3088.49±155.27	3062.32±603.23	NS	NS
Birth weight (g) ±SD (<37 weeks)	2954.64±293.22	3015.73±431.27	3002.44±284.32	NS	NS
Low birth weight (<2500g) (%)	7 (12.1)	6 (7.7)	6 (12.0)	NS	NS
Very low birth weight (<1500g) (%)	3 (5.2)	3 (3.8)	3 (6.0)	NS	NS

(S). Pregnancies following ART with male factor infertility diagnosis (I). Spontaneously conceived pregnancies (II). Pregnancies following ART with other infertility diagnosis NS: No significance *n=Number of neonates

hospitalization in all subgroups were similar (P: 0.63 for singletons, P: 0.49 for twins).

In the study group, one infant with hypospadias, one with annular pancreas, and one with central nervous system malformation were observed. In the control group I, there were one infant with heart malformation, two with cleft lips, and two with limb anomalies. One trisomy 21 fetus in the study, and one, in the control group I, had been confirmed after prenatal diagnosis and both of them had been terminated in 19th weeks of gestation. There were no perinatal deaths in both groups, whereas, four immature deaths were observed in the study group.

Pregnancies following ART with male factor infertility diagnosis versus pregnancies following ART with other infertility diagnosis

One hundred eight pregnancies were included in the control group II; 77 singletons (71%), 25 twins (23.14%), and 6 triplets (5.5%).

Birth weights and duration of gestation were found similar among both singletons and twins. Both singletons and twins of the study group had a risk of low birth weight at term that was similar with singletons and twins of the control group II. They had also no significant increase in the risk of preterm low birth weight (Tables 3 and 4).

No statistically significant differences in the rates of most obstetric complications between the study group and the control group II were observed. Because gestational diabetes mellitus, gestational hypertension, placental pathologies, amnion fluid disorders, and intrauterine growth restrictions were observed in only few cases, they were not analyzed in subgroups. The neonatal outcomes were similar in both groups. There were no significant differences in the incidence, indication and duration of the neonatal intensive care unit hospitalization for both singletons and twins. In the control group II, there was one infant with hypospadias and one with duodenal stenosis. One trisomy 21 fetus in the control group II had been terminated in 19th weeks of gestation after prenatal diagnosis. There were two immaturity related deaths in the control subjects.

DISCUSSION

Despite the reputation of ART, as enabling conceptions for couples with fertility problems,

reports of birth defects and health problems in children born of ART have led to concerns about the safety of these techniques^(1, 2). Retrospective and prospective follow-up studies of infants born as a result of these technologies have shown that neonatal outcomes and malformation rates were not different from those of general population, except for LBW, even in singleton pregnancies⁽⁷⁾. However, some reports have suggested an increased risk of major birth defects⁽⁸⁾, while others have suggested increased risk of neurological problems, especially cerebral palsy⁽⁹⁾.

In the present study, the overall obstetric and perinatal outcomes of pregnancies following

ART with male factor infertility diagnosis were similar to spontaneously conceived pregnancies. In addition, an elevated rate of adverse maternal and fetal outcomes found in other studies has been eliminated by carefully choosing matched controls. Women who conceive after ART are usually older, primiparous, and have poorer obstetric history than their peers who conceive naturally. These features are all predictive of increased obstetric risk and adverse outcome. Therefore, a comparison with a matched control group of women who conceived spontaneously is mandatory for evaluating whether the obstetric outcome of ART pregnancies is different from that of natural conceptions^(10-13 and 14). In our study, women were matched considering important characteristics that may have impact on the pregnancy outcomes, such as maternal ethnicity, age, parity, weight, height, smoking habits, medical illness, obstetric history, location, date, and mode of delivery. Because most subjects gave birth in the same obstetric units, the same medical staff following the same protocols managed them.

In the study, according to adjusted reanalysis, singletons conceived with ART following male factor infertility that were born either at term or preterm, were not at increased risk for LBW compared to natural conceptions. Singletons weighing <2500 g were more common among

ART children than controls in both matched^(10-14, 17-22 and 23) and non-matched^(24, 25) studies; but our study did not confirm these results. Birth weights of twins conceived with

ART with male factor infertility that were born either at term or at preterm, were also not lower than twins of the natural conceptions. Our results are in agreement with previous studies in twin pregnancies^(10, 12, 14, 18-21, and 26) and not confirming Minakami H, et al. who

found lower risks of adverse outcome in twins conceived by ART⁽²⁷⁾. Schieve et al.⁽⁷⁾, have also stratified analysis for the singletons, and twins. This evaluation revealed that only singletons were at an increased risk, whereas twins had a risk ratio of 1.0. This finding is contradictory to the theory that ART is responsible. If embryos conceived through ART were truly at an increased risk for restricted growth, we would have expected this risk to be accentuated in the relatively compromised environment of a uterus with multiple gestations.

We did not find an increased risk for any obstetric complications in ART pregnancies with male factor infertility compared to spontaneously conceived pregnancies. Several studies have reported debatable data concerning the rate of obstetric complications during the course of ART pregnancies^(14, 17). This inconsistency results most probably from differences in study designs. Some studies having similar findings to our study showed that ART pregnancies did not carry increased risks for obstetric complications^(15, 16). However, in contrast to our results, Tan et al. found significantly increased incidence of placenta previa, hypertension requiring hospitalization and intrauterine growth restriction among the IVF pregnancies⁽¹⁴⁾. We used a matching method in which the patients were matched based on ten variables as opposed to the single-variable stratum-matching method used by Tan et al⁽¹⁴⁾. Various matched and non-matched studies have shown that children born after ART have more neonatal problems and need longer hospitalization and intensive care than spontaneously conceived ones^(12, 18, 20-30). In spite of the strong effect of multiplicity on neonatal outcomes, children from singleton ART pregnancies also seem to be more predisposed to adverse neonatal outcomes such as preterm birth, LBW, and longer hospitalization than other children^(11-13, 15, 17- 21, and 24). The neonatal outcomes of ART pregnancies in the present study were comparable to the outcomes of natural conceptions. The rate of neonatal intensive care unit admissions, perinatal morbidity, and mortality were not significantly different. This is in agreement with previous reports of similar perinatal mortality rates for ART deliveries in comparison with maternal agestandardized rates^(3, 14, and 31).

While some recent studies have found an increased rate of some congenital anomalies among newborns

conceived by IVF^(8, 32, and 33), these were not apparent in our study, confirming another study⁽³¹⁾. Hansen et al. suggested that the increase in risk might be associated with the treatment; however, they acknowledge that confounding factors due to underlying causes of infertility could not be eliminated⁽⁸⁾. An appropriate control population of babies born to infertile women achieving pregnancy without the use of ART would have eliminated this major weakness. However, the increased risk of congenital anomalies in these large studies can partly be explained by the characteristics of women undergoing IVF, e.g. age, parity, multiple pregnancy, and duration of infertility. Some authors have also suggested an increased risk of congenital anomalies after ICSI⁽³⁾. The rate of congenital anomalies was not elevated in our study, although almost all procedures applied were ICSI (97%). In many cases potentially related to the increased risk of fetal defects, a high incidence of chromosomal abnormalities has been reported in infertile males^(34, 35, 36), as well as delayed DNA replication of paternal genome after ICSI that could also be responsible for aneuploidies⁽³⁷⁾. However, the higher overall aneuploidy rate of 11.4 % reported by Palermo et al.⁽³⁶⁾ was observed in men with non-obstructive azoospermia compared to 1.8 % in men with obstructive azoospermia, a critical distinction for genetic counseling in these patients. In addition to the ART, infertility itself contributes to increased obstetric risks⁽³⁸⁾.

Therefore, while interpreting the current data we cannot speculate that gamete or embryo manipulation or infertility treatments are the sole cause of these complications. Suggested associations in some studies may simply be explained by one or more factors, such as an underlying infertility-related condition⁽⁴⁾. Only a few studies have been conducted to evaluate the possible differences in pregnancy complications in different infertility subgroups.

Although Isaksson et al., have reported the overall similar obstetric outcomes among couples with unexplained infertility compared with spontaneous and IVF pregnancies generally⁽⁵⁾, Wang. et al. have found LBW among couples with unexplained infertility compared with other causes of infertility⁽³⁹⁾. All births occurred in the study group, and matching controls were elective or emergent cesarean sections. Considering the comparable rates of most antenatal complications, it seems reasonable to assume that the

high rate of cesarean sections among ART patients was, at least in part a reflection of the increased anxiety surrounding the management of these premium pregnancies.

Meanwhile, in Turkey, ART was not included in standard medical insurance coverage in the study period, so ART treatment was not equally available to all socioeconomic classes.

In order to determine whether a cause and effect relationship exists between the processes of ART and a specific outcomes, the proper control population should be chosen from babies born to infertile couples achieving pregnancies without use of ART. In conclusion, we should emphasize that, even if the described adverse relationships are precise, for infertile couples, absence of offspring may represent a greater personal disaster than a presumed risk of having an affected child.

By emphasizing on male factor, we excluded the effect of female infertility status and possible adverse in-vivo environment for embryo development and the study revealed solely the effect of the ART treatment with paternal contribution. However, the overall perinatal outcomes of couples with male factor infertility did not differ from other infertile couples.

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