

# CLINICAL ASSISTED REPRODUCTION

## Are Singleton Assisted Reproductive Technology Pregnancies at Risk of Prematurity?

T. PERRI,<sup>1</sup> R. CHEN,<sup>1</sup> R. YOELI,<sup>1</sup> P. MERLOB,<sup>2</sup> R. ORVIETO,<sup>1</sup> Y. SHALEV,<sup>1</sup> Z. BEN-RAFAEL,<sup>1</sup> and I. BAR-HAVA<sup>1,3</sup>

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**Purpose:** Our purpose was to determine the risk of premature delivery among singleton pregnancies derived from assisted reproduction technology (ART).

**Methods:** Ninety-five singleton ART pregnancies and 190 matched spontaneous pregnancies were assessed for preterm delivery rates, pregnancy complications, and cesarean section rates in a retrospective study at an academic medical center.

**Results:** Among the ART singleton deliveries group (n = 95), 19 (20%) were preterm, which was statistically significantly higher than the 4% (8 of 190) found in the control group. Among the pregnancies achieved by intracytoplasmic sperm injection (ICSI) in the severe male-factor infertility subgroup (n = 22), only one preterm delivery occurred (4.5%).

**Conclusions:** Singleton ART pregnancies are at an increased risk of preterm delivery compared to singleton pregnancies after spontaneous conception. The higher rate may be attributed to various infertility cofactors, such as uterine malformations, previous operative procedures that involved cervical dilatation, and a history of pelvic infection. This is supported by the finding that ICSI-derived pregnancies in couples with strict male-factor infertility are not at an increased risk of preterm delivery.

**KEY WORDS:** preterm delivery; singleton pregnancy.

<sup>1</sup> Department of Obstetrics and Gynecology, Rabin Medical Center, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

<sup>2</sup> Department of Neonatology, Rabin Medical Center, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

<sup>3</sup> To whom correspondence should be addressed at Rabin Medical Center, Golda Campus, Petah Tiqva 49372, Israel. Fax: 972-3- 937 2512. E-mail: barhava@ccsg.tau.ac.il

## INTRODUCTION

Assisted reproduction technology (ART) is associated with a high rate of multiple pregnancies. This constitutes the major risk factor of such treatment owing to their high rate of complications, especially prematurity. Whether singleton ART-derived pregnancies are also at high risk of prematurity remains controversial. Some authors have reported higher rates of prematurity in singleton ART pregnancies than in spontaneous pregnancies (1–10), whereas others found no such difference (11–13).

The aim of the present study was to compare the risk of preterm labor among singleton ART [*in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI)] pregnancies with that of spontaneously conceived ones. Both a cohort and a case control analysis were performed.

## MATERIALS AND METHODS

The analysis included only pregnancies that led to live births (>23 completed gestational weeks). Prematurity was defined as birth before 37 completed weeks of gestation. For the ART pregnancies, gestational age was calculated by the ovum pickup day (defined as two completed weeks of gestation) and verified by a first-trimester ultrasound. For the spontaneously conceived pregnancies, gestational age at delivery was calculated by the last menstrual period and verified by a first-trimester ultrasound.

The study population included 95 singleton ART-derived pregnancies, of which 42 were achieved by IVF, 51 by ICSI, and the remainder by transferring both IVF- and ICSI-derived embryos. The ovarian stimulation protocol, ultrasound and hormonal surveillance methods, hCG timing, oocyte retrieval technique, and embryo culture methods were similar in both the IVF and the ICSI cycles. These details and the laboratory technique for standard IVF and our methodology for ICSI have all been described previously (14). ICSI was carried out whenever the couple fulfilled one of the following criteria: (a) poor semen characteristics (<5 million total motile sperm in the ejaculate before processing) or (b) a <30% fertilization rate in a previous standard IVF cycle. Embryo morphology was graded before embryo transfer. Cleaving embryos were selected for transfer or freezing on the basis of their morphological score. All embryos were left in culture until the embryo transfer day.

All data were prospectively collected on a computerized database. Informed consent was obtained from all patients.

**Phase 1: Cohort analytic study.** The incidence of preterm delivery among the study group was compared with that of all consecutive singleton deliveries performed at the Rabin Medical Center in 1996. The latter were collected from the prospectively created database of the Neonatology Unit.

**Phase 2: Case-control study.** The control group consisted of 190 spontaneously conceived singleton pregnancies with delivery at our center within the same time frame as the study group. All 95 ART-derived pregnancies were matched in a 1:2 fashion to the next two spontaneous pregnancies for maternal age ( $\pm 2$  years), ethnic origin, gravidity, and parity. The two groups were then compared for rate of preterm delivery. These data for phase 2 were obtained from our ART computerized database and our labor and delivery logbooks.

A comparison was also made between the preterm and full-term deliveries within the ART group for route of delivery and possible risk factors of prematurity.

For statistical analysis the  $\chi^2$  test or Fisher's exact probability test and Student's *t*-test were used as appropriate.

## RESULTS

**Phase 1.** There were 2546 singleton live-born deliveries in our center during 1996, of which 185 (7.3%)

**Table I.** Preterm Delivery Rates in the Study Groups (Phase 1)

Phase	ART pregnancies	Spontaneous pregnancies	<i>P</i> value ( $\chi^2$ )
Cohort study	19/95 (20%)	185/2546 (7.3%)	<0.001
Case-control study	19/95 (20%)	8/190 (4%)	<0.001

were preterm. Twenty labors (11%) occurred at weeks 23–29, 39 (21%) at weeks 30–33, and 126 (68%) at weeks 34–36. Among the 95 ART pregnancies, 19 (20%) were preterm: 7 (37%) at weeks 30–33 and 12 (63%) at weeks 34–36. The difference in the rate of prematurity between the groups was statistically significant ( $P < 0.001$ ) (Table I).

**Phase 2.** The 95 ART deliveries were matched with 190 controls. The mean maternal age for the ART and control groups was similar ( $32.15 \pm 4.5$  and  $32.13 \pm 4.5$  years, respectively). The median gravidity was 2 (range, 1–6) and the median parity was 0.4 (range, 0–2) for both groups. There were 82 and 164 Jewish patients and 13 and 26 Arabic patients in the ART and control groups, respectively.

Within the ART group, the indications for IVF or ICSI included tubal sterility (14%), endometriosis (5%), male-factor infertility (39%; 19% with severe male factor, i.e., <5 million motile sperm in the ejaculate), unexplained infertility (28%), polycystic ovary syndrome (8%), and other female disorders (6%); 21% had more than a single indication.

In the ART group, the mean gestational age at delivery was  $38.3 \pm 2.5$  weeks. Of the 19 preterm labors (20%), 9 of 42 (21.4%) were in the IVF subgroup and 10 of 51 (19.6%) in the ICSI subgroup. Only one preterm delivery occurred among the patients treated with ICSI for strict male-factor infertility (<5 million motile sperm in the ejaculate) ( $n = 22$ ; 4.5%). In the control group, the mean gestational age at delivery was  $39.1 \pm 3.07$  weeks, and preterm delivery occurred in eight pregnancies (4%). The difference from the study group was statistically significant ( $P < 0.001$ ) (Table I). Ten (50%) of the premature deliveries in the ART group were induced (either vaginally or by cesarean section). Reasons for interventions included severe hypertension (two cases), intrauterine growth restriction (IUGR) (one case), abnormal findings on fetal heart rate monitoring (two cases), and a severe bleeding episode with suspected abruption placentae (five cases). In the control group, four of the preterm deliveries (50%) were induced, one because of IUGR and oligohydramnios, two for abruption placentae, and one because of abnormal findings on fetal heart rate monitoring. It should be noted that, even

**Table II.** Distribution of Risk Factors for Prematurity Among Preterm and Term Singleton ART Deliveries<sup>a</sup>

Risk factor	Preterm ( <i>n</i> = 19)	Term ( <i>n</i> = 76)	<i>P</i> (Fisher's test)
Smoking	2 (10.5%)	12 (15.8%)	NS
Amniocentesis in current pregnancy	6 (31.6%)	23 (30.3%)	NS
Previous artificial abortion	1 (5.3%)	5 (6.6%)	NS
Previous spontaneous abortion	4 (21%)	25 (33%)	NS
Cerclage in current pregnancy	2 (10.5%)	7 (9.2%)	NS
Previous extrauterine pregnancy	1 (5.3%)	9 (11.8%)	NS

<sup>a</sup> Values are actual numbers and percentages (in parentheses) of the total number of ART deliveries (preterm and term).

when removing the induced preterm deliveries from our data, there was still a significant difference between the groups in the spontaneous preterm delivery rate (11.7 and 2.19% for the ART and control groups; respectively;  $P < 0.01$ ).

The ART patients who delivered before term did not differ from those who delivered at term in incidence of smokers, previous abortions, amniocentesis rate, or incidence of cervical cerclage (Table II). Rates of pregnancy-induced hypertension and gestational diabetes were similar in these ART subgroups, but the preterm subgroup had significantly more cases of placental complications (placenta previa and abruption) than the term subgroup (Table III). In the single case of IUGR in the preterm group, it was the presence of IUGR that led to the induction of delivery prematurely. Routes of delivery are presented in Table IV. Cesarean section rates were 42.1% ( $n = 40$ ; 13 elective and 27 emergent) and 20.5% ( $n = 39$ ; 12 elective and 27 emergency) in the ART and control groups, respectively. The difference was statistically significant (Table IV). Indications for cesarean

**Table III.** Pregnancy Complications Among Preterm and Term ART Singleton Deliveries<sup>a</sup>

Complication	Preterm ( <i>n</i> = 19)	Term ( <i>n</i> = 76)	<i>P</i> (Fisher's exact test)
PIH <sup>b</sup>	3 (15.8%)	4 (5.3%)	0.1
Placenta previa or abruption	6 (31.6%)	7 (9.2%)	<0.01
Gestational diabetes	2 (10.5%)	13 (17%)	0.48

<sup>a</sup> Values are actual numbers and percentages (in parentheses) of the total number of ART deliveries (preterm and term).

<sup>b</sup> Pregnancy-induced hypertension.

**Table IV.** Delivery Route in the Case–Control Study Groups (Phase 2)<sup>a</sup>

Delivery route	ART pregnancies ( <i>n</i> = 95)	Spontaneous pregnancies ( <i>n</i> = 190)	<i>P</i> value ( $\chi^2$ )
Spontaneous vaginal	53 (55.8%)	139 (73.2%)	<0.01
Instrumental	2 (2.1%)	12 (6.3%)	0.12
Cesarean election			
Elective	13 (13.7%)	12 (6.3%)	0.04
Emergency	27 (28.4%)	27 (14.2%)	<0.01

<sup>a</sup> Values are actual numbers and percentages (in parentheses) of the total number of ART deliveries (preterm and term).

sections included breech presentation, suspected cephalopelvic disproportion (CPD), nonreassuring fetal heart rate monitoring, previous cesarean section, preeclamptic toxemia, macrosomia with gestational diabetes, placenta previa or placental abruption, and patient request. Comparing the indices for the various indications between both groups, the only significant differences found were regarding the rates of placental abruption [1% (2/190) vs 5.5% (5/90),  $P$  (Fisher's exact) < 0.04] and of suspicious fetal heart rate monitoring [3.15% (6/190) vs 13.33% (12/90);  $P < 0.03$ ] in the control and ART groups, respectively.

## DISCUSSION

The present study indicates that singleton ART pregnancies are at an increased risk of preterm delivery in comparison with spontaneous pregnancies (20 and 4–7.3%, respectively). These findings are concordant with some previous reports (1–10) but discordant with others (11–13), (Table V). The advantages of the present study include properly matched patient groups and the inclusion of only patients who delivered at one center within the same period of time and received similar obstetric care.

Two main factors that may contribute to the large proportion of preterm deliveries among the singleton ART-derived pregnancies are the high rate

**Table V.** Literature Summary of Pregnancy Complications in ART and Spontaneous Singleton Pregnancies

Complication	Ref. No.(s.)
Increased rate of preterm deliveries in ART	1–10
Increased rate of PIH in ART	3,9,18
Increased rate of gestational diabetes in ART	18
Increased CS rate in ART	2–5,7,9, 11–13,18
No difference in prematurity rate	11–13

of primiparas and advanced maternal age, both characteristic of the ART-treated population in general. However, these factors were well controlled by our study design.

A history of uterine anomaly, pelvic procedure, previous abortion(s), operative hysteroscopy, and pelvic infection are all considered risk factors for infertility as well as for preterm delivery. Therefore, a high incidence of preterm delivery would be expected among IVF patients with mechanical infertility but not ICSI patients, who have "pure" male-factor infertility. This was corroborated in the present study. Our 4.5% incidence of preterm delivery in the ICSI-derived pregnancies was similar to that in the spontaneous pregnancy population. Better obstetric results with ICSI singletons compared to standard IVF singletons were also shown by Wennerholm *et al.* (12) and Wisanto *et al.* (15). These data, however, agree only in part with the study of Govaerts *et al.* (16), who compared 145 ICSI pregnancies with 145 matched IVF controls, of which 65% were singletons. They found a similar mean gestational age for both groups, but a significantly higher mean gestational age for ICSI-derived twins.

Some authors have speculated that the supraphysiological levels of sex hormones (estrogen, progesterone, and insulin growth factor I) during ovulation induction, implantation, and early pregnancy may contribute to premature delivery (4,17). This abnormal hormonal environment may be even more pronounced if ovulation induction is complicated by ovarian hyperstimulation syndrome. Furthermore, high levels of  $\beta$ -hCG have also been reported throughout the first half of ART-derived pregnancies (18). High  $\beta$ -hCG levels are known to be associated with a higher incidence of some pregnancy complications, such as placental abnormalities and spontaneous preterm delivery (19). Therefore, it may be postulated that the present findings are at least partly attributable to these factors.

One of the assumed mechanisms of a significant proportion of preterm deliveries is intrauterine asymptomatic infection (20,21). Therefore, another possible contributory factor to the increased incidence of preterm delivery in singleton ART-derived pregnancies is the IVF technique itself. Both the oocyte retrieval and the embryo transfer procedures may lead to ovarian and cervical trauma, which may in turn cause bleeding and subsequent pelvic (including uterine) infection (3). This may be even more relevant in patients with mechanical infertility, such as that caused by chronic chlamydial infection.

However, when the data for maternal age, parity, previous subfertility, and year of birth were stratified, Bergh *et al.* (1) found no relationship between the IVF technique and the rate of preterm deliveries.

Another possible explanation is the increased incidence of pregnancy complications in ART, as observed in the present study, resulting in a high rate of induced preterm deliveries. However, findings in the literature are contradictory. The FIVNAT study (6) and several case-control studies (5,7,11) noted similar rates of pregnancy-induced hypertension in ART pregnancies and spontaneous conceptions. Maman *et al.* (17), however, reported a significantly higher rate of pregnancy-induced hypertension in the IVF group (OR = 2.1). In agreement with the former, our data demonstrate similar rates of pregnancy-induced hypertension among the preterm and term ART pregnancies [3/19 (15.8%) vs 4/76 (5.3%) respectively,  $P = 0.1$ ]. Concerning antenatal bleeding, Rubinoff *et al.* (11) and Verlaenen *et al.* (5) reported similar rates in IVF and spontaneous singleton conceptions, whereas we found a significantly higher rate of placental complications (placenta previa and placental abruption), which led to induction of premature deliveries among the IVF singleton pregnancies.

ART-derived pregnancies are usually achieved after a prolonged and devastating infertility period and exhaustive treatment, and it is reasonable to assume that clinical decisions may be influenced by the anxiety and stress expressed by the women, family, and friends. The high rate (58%) of preterm cesarean sections detected in the present study may at least in part reflect these circumstances. A high cesarean section rate among ART-derived pregnancies has been reported by other authors as well (2-5,7,9,11-13,17).

Our data indicate that ART-derived pregnancies are associated with an increased risk of prematurity, except for those patients with "pure" male-factor infertility. Therefore, we suggest that all women with singleton ART-derived pregnancies should be carefully observed throughout pregnancy for the detection and prompt treatment of complications. Since the present study was retrospective in nature, we are currently conducting a prospective study in our unit to explore these issues further.

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