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## ARTICLE

# Maternal and neonatal health outcomes following assisted reproduction

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**Abstract** This study assessed the risk for maternal complications in women and neonatal outcomes in children conceived following assisted reproductive treatment as compared with spontaneously conception and also separately evaluated conventional IVF and intracytoplasmic sperm injection (ICSI). The prospective cohort included 1161 women with singleton pregnancies: 561 who conceived following assisted reproduction (223 following IVF and 338 following ICSI) and 600 who conceived spontaneously. No differences were observed in pregnancy complications (including spontaneous abortion, pregnancy-induced hypertension, gestational diabetes and Caesarean delivery) except for significantly increased risk for excess vaginal bleeding in assisted reproduction pregnancies (21.4% versus 12.9%; OR 1.67, 95% CI 1.18–2.37), which was prominent in women who reported polycystic ovary syndrome. Neonates born following assisted reproduction had increased risk for prematurity (10.6% versus 5.3%; OR 1.72, 95% CI 1.04–2.87), and IVF, but not ICSI, was associated with significantly increased risk for prematurity (OR 2.36, 95% CI 1.28–4.37) and low birthweight (OR 1.89, 95% CI 1.03–3.46). In conclusion, this study observed only an increased risk for excess vaginal bleeding as a pregnancy-associated complication in singleton pregnancies following assisted compared with spontaneous conception. However, singleton neonates born following IVF, but not ICSI, were at increased risk for prematurity. 

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**KEYWORDS:** assisted reproduction, birth outcomes, ICSI, IVF, pregnancy complications

## Introduction

Despite the widespread use of assisted reproduction treatment, there is still concern regarding the safety of these treatments to both mothers and their neonates. Although the rate of multiple births following assisted reproduction is increased as compared with spontaneously conceived pregnancies and complications following multiple births are well known (McDonald et al., 2005), singleton assisted reproduction pregnancies are also at increased risk for adverse pregnancy outcome compared with spontaneously conceived singleton pregnancies, as reported in two systematic reviews (Helmerhorst et al., 2004; Jackson et al., 2004). These include an increased risk for preterm birth (<37 weeks), low birthweight (<2500 g) and very low birthweight (<1500 g), small-for-gestational-age and Caesarean delivery. In addition, Jackson et al. (2004) reported increased risk for maternal complications including placenta praevia, vaginal bleeding, pre-eclampsia and gestational diabetes mellitus.

Although maternal age and parity were usually adjusted in these analyses, data regarding other potential confounders such as past obstetric outcome, medical history, infertility (type and treatment), smoking, educational level and body mass index (BMI) are limited.

In Israel, assisted reproduction treatment is funded in the framework of the national health insurance for the first two children, with no limitation on the number of treatment cycles for women up to the age of 45. Currently, 4.2% of all live births in Israel are conceived following assisted reproduction and the percentage is rising (Department of Health Information, Ministry of Health, Israel, 2010). Considering recent concerns (Helmerhorst et al., 2004; Jackson et al., 2004; McDonald et al., 2009) and the increasing number of children born following assisted reproduction, this study was designed to evaluate the risks for maternal and neonatal complications following assisted reproduction treatment as compared with spontaneously conceived pregnancies, as well as conventional IVF and intracytoplasmic sperm

injection (ICSI) compared with spontaneously conceived pregnancies.

## Materials and methods

The prospective cohort was composed of singleton pregnancies following assisted reproduction and spontaneously conceived singleton pregnancies. Women were identified at 6–12 weeks of gestation, during ultrasound examination at the two participating IVF units (Sheba Medical Centre and Assaf Harofeh Medical Centre). Spontaneously conceived pregnancies were recruited at five community women's healthcare centres and at the two participating medical centres. Of these, 133 women were identified during ultrasound examination at 6–12 weeks of gestation. In addition, 467 women with singleton live birth were randomly selected from the delivery room records and recruited by telephone call following delivery hospitalization. Only women demonstrating one gestational sac with a fetal heart pulse were included in the study.

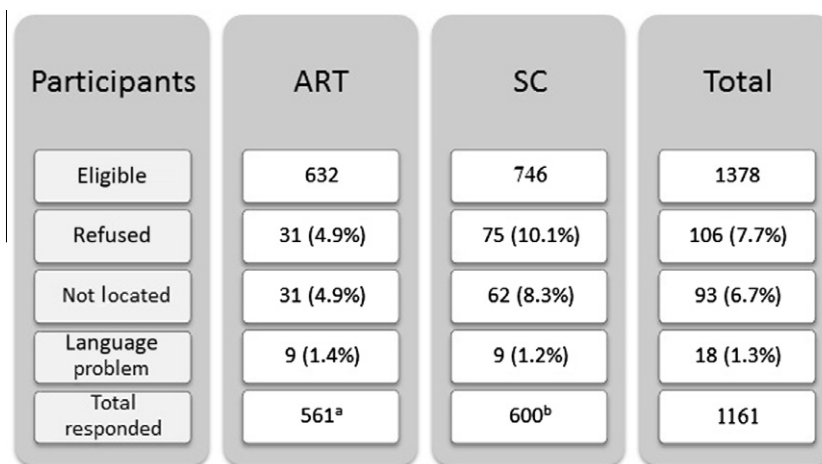
All women were recruited from June 2006 to December 2008. Telephone interviews were conducted 6 weeks following delivery.

## Study population

The final cohort was composed of 1161 women with singleton pregnancies. A flow chart of patient participation in the study is presented in Figure 1.

## Questionnaire and variables

The telephone interview 6 weeks following delivery included demographic (age, education), medical history (hypertension, diabetes, asthma, malignancy, epilepsy) and obstetric history (number of abortions, number of live births) as well as details regarding the current pregnancy, including spontaneous abortion (defined as loss of



**Figure 1** Flow chart of the study population.

<sup>a</sup> = 223 women recruited following IVF (40%) treatment and 338 (60%) women following ICSI treatment;

<sup>b</sup> = 133 women with one gestational sac and one heart beat recruited following ultrasound examination at 8–12 gestational weeks together with 467 women with singleton live birth recruited randomly from hospital records post delivery. ART = assisted reproduction treatment; ICSI = intracytoplasmic sperm injection; SC = spontaneous conception.

pregnancy before 20 weeks gestation), lifestyle during pregnancy (folic acid use: yes/no; smoking: yes/no; BMI: <18, 19–24, 25–29, >30 kg/m<sup>2</sup>), pregnancy complications (vaginal bleeding: yes/no, if yes, trimester and duration of bleeding; pregnancy-induced hypertension: yes/no, if yes, treatment; gestational diabetes: yes/no, if yes, treatment), outcome of the pregnancy including mode of delivery (Caesarean section, yes/no), preterm birth (<37 weeks), low birthweight (<2500 g), small-for-gestational-age (birthweight <10th percentile for gestational age according to

gender-specific charts (Kramer et al., 2001)) and congenital malformations (yes/no). All the variables were collected during telephone interview with the mother.

For women who conceived following assisted reproduction, additional questions relating to infertility included: type of treatment (IVF or ICSI), infertility diagnosis (male factor, polycystic ovary syndrome (PCOS), hormonal, tubal infertility, other/unexplained), previous assisted reproduction treatment (yes/no), number of embryos transferred (1, 2, 3, 4+) and type of embryo (fresh or frozen).

**Table 1** Maternal characteristics according to mode of conception (N = 1161).

|                          | Spontaneous<br>conception<br>(n = 600) | All assisted<br>reproduction<br>(n = 561) | P-value | IVF (n = 223) | ICSI (n = 338) | P-value |
|--------------------------|----------------------------------------|-------------------------------------------|---------|---------------|----------------|---------|
| Age (years)              |                                        |                                           | <0.0001 |               |                | 0.0005  |
| 17–25                    | 90 (15.0)                              | 31 (5.5)                                  |         | 5 (2.2)       | 26 (7.7)       |         |
| 26–30                    | 187 (31.2)                             | 137 (24.4)                                |         | 44 (19.7)     | 93 (27.5)      |         |
| 31–35                    | 216 (36.0)                             | 222 (39.6)                                |         | 90 (40.4)     | 132 (39.1)     |         |
| 36–40                    | 94 (15.7)                              | 130 (23.2)                                |         | 59 (26.5)     | 71 (21.0)      |         |
| 41+                      | 13 (2.2)                               | 41 (7.3)                                  |         | 25 (11.2)     | 16 (4.7)       |         |
| Education (years)        |                                        |                                           | <0.0001 |               |                | NS      |
| 6–12                     | 174 (29.0)                             | 223 (40.1)                                |         | 93 (42.3)     | 130 (38.7)     |         |
| 13+                      | 426 (71.0)                             | 333 (59.9)                                |         | 127 (57.7)    | 206 (61.3)     |         |
| Unknown                  | —                                      | 5                                         |         | 3             | 2              |         |
| Obstetric history        |                                        |                                           | <0.0001 |               |                | NS      |
| First pregnancy          | 174 (29.0)                             | 221 (39.4)                                |         | 90 (40.4)     | 131 (38.8)     |         |
| Previous live births     | 251 (41.8)                             | 145 (25.8)                                |         | 52 (23.3)     | 93 (27.5)      |         |
| Previous abortions       | 175 (29.2)                             | 195 (34.8)                                |         | 81 (36.3)     | 114 (33.7)     |         |
| Prior to pregnancy       |                                        |                                           |         |               |                |         |
| Medical history          |                                        |                                           |         |               |                |         |
| Hypertension             | 4 (0.7)                                | 9 (1.6)                                   | NS      | 5 (2.2)       | 4 (1.2)        | NS      |
| Diabetes                 | 3 (0.5)                                | 10 (1.8)                                  | 0.04    | 6 (2.7)       | 4 (1.2)        | NS      |
| Asthma                   | 34 (5.7)                               | 23 (4.1)                                  | NS      | 6 (2.7)       | 17 (5.0)       | NS      |
| Malignancy               | 3 (0.5)                                | 11 (2.0)                                  | 0.02    | 6 (2.7)       | 5 (1.5)        | NS      |
| Epilepsy                 | 2 (0.3)                                | 7 (1.2)                                   | NS      | 3 (1.3)       | 4 (1.2)        | NS      |
| BMI (kg/m <sup>2</sup> ) |                                        |                                           | NS      |               |                | NS      |
| <18                      | 29 (5.2)                               | 24 (4.4)                                  |         | 9 (4.1)       | 15 (4.6)       |         |
| 19–24                    | 358 (64.5)                             | 331 (60.4)                                |         | 129 (58.1)    | 202 (62.0)     |         |
| 25–29                    | 129 (23.2)                             | 130 (23.7)                                |         | 53 (23.9)     | 77 (23.6)      |         |
| 30+                      | 39 (7.0)                               | 63 (11.5)                                 |         | 31 (14.0)     | 32 (9.8)       |         |
| Unknown                  | 45                                     | 13                                        |         | 1             | 12             |         |
| During pregnancy         |                                        |                                           |         |               |                |         |
| Smoking                  | 49 (8.2)                               | 37 (6.6)                                  | NS      | 19 (8.5)      | 18 (5.3)       | NS      |
| Folic acid use           |                                        |                                           | <0.0001 |               |                | NS      |
| No use                   | 107 (17.8)                             | 37 (6.7)                                  |         | 15 (6.8)      | 22 (6.6)       |         |
| Not every day            | 94 (15.7)                              | 97 (17.5)                                 |         | 32 (14.5)     | 65 (19.4)      |         |
| Every day                | 396 (66.0)                             | 421 (75.9)                                |         | 173 (78.6)    | 248 (74.0)     |         |
| Unknown                  | 3                                      | 6                                         |         | 3             | 3              |         |

Values are n (%). Percentages were calculated without missing values.

BMI = body mass index; ICSI = intracytoplasmic sperm injection; NS = not statistically significant.

## Statistical analysis

Differences between assisted conception and spontaneously conceptions and between IVF and ICSI were tested using the chi-squared test for categorical variables and by *t*-test for continuous variables. All tests were two tailed and *P*-values <0.05 were considered statistically significant. Logistic regression analyses were used to assess the independent effect of treatment exposure on the adverse outcomes with adjustment for confounding variables. Complications during pregnancy were adjusted for maternal age, education, obstetric history, hypertension and diabetes prior to pregnancy, BMI prior to pregnancy and smoking during pregnancy. Pregnancy outcome was also adjusted for pregnancy complications (vaginal bleeding, pregnancy-induced hypertension, gestational diabetes).

For the comparison between ICSI and IVF treatment groups, adjustments in addition to the above were performed for infertility diagnosis, previous treatment cycles, type of embryo and number of embryos transferred. Crude and adjusted odds ratios (OR) are presented with 95% confidence intervals (CI). Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

## Ethical approval

Approval was obtained from the two participating medical centres (Sheba Medical Centre, 3657/05 on 26 April 2005; Assaf Harofeh Medical Centre, 129/05 on 10 November 2005).

## Results

The prospective cohort was composed of 1161 women: 561 women pregnant following assisted reproduction, of whom 52 terminated with abortions (45 spontaneous and seven induced) and 509 births, including one stillbirth. The spontaneous conception group included 600 women: 467 recruited during their post-delivery hospitalization and 133 recruited at the beginning of pregnancy, of whom 11 had spontaneous abortions and two had induced abortions, resulting in a total of 587 live births.

The maternal characteristics of the two groups are compared in Table 1. Women in the assisted reproduction group were significantly older (mean  $\pm$  SD age  $33.1 \pm 4.9$  versus  $30.1 \pm 4.9$  years,  $P < 0.001$ ) and less educated compared with the spontaneous conception group. BMI at the beginning of pregnancy was slightly higher in the assisted reproduction group than in the spontaneous conception group ( $23.8 \pm 5.1$  versus  $22.9 \pm 4.2$  kg/m<sup>2</sup>,  $P = 0.003$ ). The ICSI-treated women were significantly ( $P = 0.0005$ ) younger than those who underwent IVF treatment. The infertility and treatment characteristics of the IVF and ICSI treatment groups are shown in Table 2. Male factor infertility was present in 61.0% of ICSI couples compared with 29.6% in the IVF group.

## Abortions

Data on abortions was available for the women who were recruited during the first trimester (554 assisted reproduc-

**Table 2** Infertility and treatment characteristics (N = 561).

|                                    | IVF<br>(n = 223) | ICSI<br>(n = 338) |
|------------------------------------|------------------|-------------------|
| Previous treatment cycles          |                  |                   |
| No                                 | 90 (40.9)        | 127 (37.7)        |
| Yes                                | 130 (59.1)       | 210 (62.3)        |
| Unknown                            | 3                | 1                 |
| Number of embryos transferred      |                  |                   |
| 1                                  | 18 (8.1)         | 22 (6.5)          |
| 2                                  | 134 (60.6)       | 217 (64.4)        |
| 3                                  | 55 (24.9)        | 76 (22.6)         |
| 4–5                                | 14 (6.3)         | 22 (6.5)          |
| Unknown                            | 2                | 1                 |
| Type of embryos                    |                  |                   |
| Fresh                              | 149 (66.8)       | 235 (69.5)        |
| Frozen                             | 74 (33.2)        | 103 (30.5)        |
| Infertility diagnosis <sup>a</sup> |                  |                   |
| PCOS                               | 33 (14.8)        | 37 (10.9)         |
| Hormonal                           | 8 (3.6)          | 7 (2.1)           |
| Tubal                              | 45 (20.2)        | 32 (9.5)          |
| Male                               | 66 (29.6)        | 206 (61.0)        |
| Other                              | 71 (31.8)        | 56 (16.6)         |

Values are *n* (%). Percentages were calculated without missing values.

ICSI = intracytoplasmic sperm injection; PCOS = polycystic ovary syndrome.

<sup>a</sup> $P < 0.0001$ .

tion and 131 spontaneous conception, not including induced abortions) (Table 3). No difference was found in the crude overall spontaneous abortion rate between assisted reproduction (45/554; 8.1%) and spontaneous conception (11/131; 8.4%). No differences were found in the abortion rates according to the week at enrolment to the study, as well as after adjustment for maternal age, maternal education, obstetric history, hypertension prior to pregnancy, diabetes prior to pregnancy, BMI prior to pregnancy and smoking during pregnancy (OR 0.94, 95% CI 0.44–2.01). No significant difference was found in the spontaneous abortion rate between the IVF and ICSI groups adjusted for the above variables and also for infertility diagnosis, number of cycles prior to current pregnancy and number and type of embryos transferred. In this model, the specific infertility diagnosis appeared to be a risk factor for abortions (hormonal infertility OR 4.8, 95% CI 1.04–21.91; PCOS OR 1.95, 95% CI 0.7–5.6; tubal infertility OR 2.6, 95% CI 0.98–6.82; as compared with male factor infertility).

## Pregnancy complications

A significantly increased risk for vaginal bleeding during pregnancy was observed in the assisted reproduction group (OR 1.67, 95% CI 1.18–2.37) (Table 4). Furthermore, excess bleeding in assisted reproduction pregnancies compared

**Table 3** Rates and adjusted odds ratios for spontaneous abortion according to type of conception.

|                           | n/N (%)      | Adjusted odds ratio |
|---------------------------|--------------|---------------------|
| Spontaneous conception    | 11/131 (8.4) | Ref.                |
| All assisted reproduction | 45/554 (8.1) | 0.94 (0.44–2.54)    |
| IVF                       | 18/220 (8.2) | 1.04 (0.43–1.63)    |
| ICSI                      | 27/334 (8.1) | 0.89 (0.40–1.98)    |

Odds ratios adjusted for maternal age, maternal education, obstetric history, hypertension prior to pregnancy, diabetes prior to pregnancy, BMI prior to pregnancy and smoking during pregnancy. Not included are induced abortions (two in the spontaneous conception group and seven in the assisted reproduction group).

No statistically significant differences were found.

with those spontaneously conceived was statistically significant only in the first trimester (12.8% versus 7.0%,  $P < 0.001$ ).

The increased risk for pregnancy-induced hypertension was of borderline significance (OR 1.49, 95% CI 0.93–2.38). The rates of gestational diabetes, cervical incompetence and placental pathologies including placenta praevia or abruption were similar in the two groups. The risks of these complications were similar in ICSI- and IVF-conceived pregnancies. The diagnosis of PCOS was a significant risk factor for vaginal bleeding in the assisted reproduction group (OR 1.97, 95% CI 1.02–3.80).

### Delivery outcome

The rate of Caesarean deliveries was significantly higher in the assisted reproduction group (26.1% versus 21.3%

$P = 0.04$ ) (Table 5); however, this difference was not present after adjusting for maternal demographic characteristics and pregnancy complications. The reported reason for the Caesarean delivery was maternal request with no medical indication in 7.4% and 3.1% in the assisted reproduction and spontaneous conception groups, respectively. A significant excess risk for preterm deliveries (OR 1.72, 95% CI 1.04–2.87) was present in the assisted reproduction group compared with the spontaneous conception group. The higher risk for small-for-gestational-age in the assisted reproduction group was of borderline significance (OR 1.34, 95% CI 0.97–1.83). Comparison of birth outcome of the IVF and ICSI treatment groups, with additional adjustment for infertility diagnosis, number of treatment cycles and number and type of embryos transferred, showed significantly lower risk for preterm birth (OR 0.52, 95% CI 0.27–0.99) and low birthweight (OR 0.44, 95% CI 0.22–0.87) in the ICSI-treated women. Number of cycles, number of embryos transferred and frozen or fresh embryos were not significant risk factors for preterm delivery.

The rate of reported congenital malformations at birth was slightly, although not significantly, higher in the assisted reproduction group (3.7%) as compared with the spontaneous conception group (2.2%).

### Discussion

This prospective study conducted in Israel followed women who conceived by assisted reproduction treatment in comparison to women conceiving spontaneously. This study reports three main findings. Firstly, no increased risk for spontaneous abortions was observed with assisted reproduction treatment compared with spontaneous conception. Secondly, after adjustment for maternal characteristics,

**Table 4** Rates and adjusted odds ratios for pregnancy complications according to type of conception.

|                                | n/N (%)        | Adjusted odds ratio | P-value |
|--------------------------------|----------------|---------------------|---------|
| Bleeding                       |                |                     |         |
| Spontaneous conception         | 76/587 (12.9)  | Ref.                |         |
| All assisted reproduction      | 109/509 (21.4) | 1.67 (1.18–2.37)    | 0.004   |
| IVF                            | 47/202 (23.3)  | 1.79 (1.14–2.81)    | 0.01    |
| ICSI                           | 62/307 (20.2)  | 1.60 (1.09–2.36)    | 0.02    |
| Pregnancy-induced hypertension |                |                     |         |
| Spontaneous conception         | 39/587 (6.6)   | Ref.                |         |
| All assisted reproduction      | 57/509 (11.2)  | 1.49 (0.93–2.38)    | NS      |
| IVF                            | 25/202 (12.4)  | 1.63 (0.89–2.99)    | NS      |
| ICSI                           | 32/307 (10.4)  | 1.41 (0.84–2.38)    | NS      |
| Gestational diabetes           |                |                     |         |
| Spontaneous conception         | 59/587 (10.1)  | Ref.                |         |
| All assisted reproduction      | 61/509 (12.0)  | 1.00 (0.65–1.54)    | NS      |
| IVF                            | 27/202 (13.4)  | 1.01 (0.58–1.78)    | NS      |
| ICSI                           | 34/307 (11.1)  | 0.99 (0.61–1.61)    | NS      |

Odds ratios adjusted for maternal age, maternal education, obstetric history, hypertension prior to pregnancy, diabetes prior to pregnancy, BMI prior to pregnancy and smoking during pregnancy.

NS = not statistically significant.



**Table 5** Rates and adjusted odds ratios for delivery outcome according to type of conception.

|                                             | n/N (%)        | Adjusted odds ratio | P-value |
|---------------------------------------------|----------------|---------------------|---------|
| <b>Caesarean delivery</b>                   |                |                     |         |
| Spontaneous conception                      | 125/587 (21.3) | Ref.                |         |
| All assisted reproduction                   | 133/509 (26.1) | 1.03 (0.75–1.41)    | NS      |
| IVF                                         | 66/202 (32.7)  | 1.31 (0.88–1.96)    | NS      |
| ICSI                                        | 67/307 (21.8)  | 0.88 (0.62–1.26)    | NS      |
| <b>Preterm delivery</b>                     |                |                     |         |
| Spontaneous conception                      | 31/587 (5.3)   | Ref.                |         |
| All assisted reproduction                   | 54/509 (10.6)  | 1.72 (1.04–2.87)    | 0.04    |
| IVF                                         | 29/202 (14.4)  | 2.36 (1.28–4.37)    | 0.006   |
| ICSI                                        | 25/307 (8.1)   | 1.40 (0.79–2.50)    | NS      |
| <b>Low birthweight</b>                      |                |                     |         |
| Spontaneous conception                      | 33/587 (5.6)   | Ref.                |         |
| All assisted reproduction                   | 50/509 (9.8)   | 1.28 (0.77–2.12)    | NS      |
| IVF                                         | 29/202 (14.4)  | 1.89 (1.03–3.46)    | 0.04    |
| ICSI                                        | 21/307 (6.8)   | 0.97 (0.53–1.75)    | NS      |
| <b>Small-for-gestational-age</b>            |                |                     |         |
| Spontaneous conception                      | 111/587 (18.9) | Ref.                |         |
| All assisted reproduction                   | 122/509 (24.0) | 1.34 (0.97–1.83)    | NS      |
| IVF                                         | 53/202 (26.2)  | 1.51 (0.99–2.28)    | NS      |
| ICSI                                        | 69/307 (22.5)  | 1.24 (0.87–1.77)    | NS      |
| <b>Congenital malformations<sup>a</sup></b> |                |                     |         |
| Spontaneous conception                      | 13/587 (2.2)   | Ref.                |         |
| All assisted reproduction                   | 19/509 (3.7)   | 1.71 (0.84–3.50)    | NS      |
| IVF                                         | 10/202 (5.0)   | 2.30 (0.99–5.33)    | NS      |
| ICSI                                        | 9/307 (2.9)    | 1.33 (0.56–3.16)    | NS      |

Adjusted for maternal age, maternal education, obstetric history, hypertension prior to pregnancy, diabetes prior to pregnancy, BMI prior to pregnancy and smoking during pregnancy.

NS = not statistically significant.

<sup>a</sup>Odds ratios for congenital malformations are unadjusted because of small numbers.

pregnancy complications were similar except for an increased risk for vaginal bleeding. Thirdly, assisted reproduction pregnancies were associated with higher risk of prematurity and low birthweight. The risk of prematurity and low birthweight occurred in the IVF rather than the ICSI pregnancies.

Spontaneous abortion is one of the pregnancy complications that is the most difficult to compare between spontaneously conceived and assisted reproduction pregnancies due to the early recognition of assisted reproduction pregnancies. In the present study, similar rates of spontaneous abortion were observed in both groups, as previously reported by others (Brandes et al., 2011; Pezeshki et al., 2000; Schieve et al., 2003). Conversely, Wang et al. (2004) compared abortion rates in IVF groups with previously reported spontaneous conception cohorts and noted significant 1.20- and 1.34-fold increased risks of abortion in the IVF group.

When analysing the IVF and ICSI groups separately, no difference in the abortion rate was observed even after

adjustment for past abortions. However, female infertility diagnoses were associated with spontaneous abortion in the adjusted model.

The following infertility diagnoses have been associated with spontaneous abortion: PCOS (Wang et al., 2001), tubal pathology and uterine infertility (Brandes et al., 2011). The type of cycle (fresh or frozen) and the number of embryos transferred did not affect the risk for abortions, as was also observed by others (Al Hasani et al., 1996). A significantly increased risk for vaginal bleeding was observed in pregnancies following assisted reproduction treatment. The only other factor associated with this risk was hypertension prior to pregnancy. Comparison between ICSI and IVF revealed that hypertension prior to pregnancy as well as infertility diagnosis of PCOS were associated with vaginal bleeding. Bleeding predominantly in the first trimester may also be due to vanishing twins. De Sutter et al. (2006), found a linear increased risk for bleeding in correlation with the number of embryos transferred. In the current study, only women with one gestational sac were included and

association was observed with the number of embryos transferred. In addition, no association with placental abruption, placenta praevia and cervical incompetence was observed, as suggested by others (Jackson et al., 2004; Katalinic et al., 2004; Shevell et al., 2005; Tan et al., 1992).

There was a higher rate of pregnancy-induced hypertension (although not significant) with assisted reproduction as compared with spontaneous conception, as also suggested by others (Kallen et al., 2005b; Katalinic et al., 2004; Maman et al., 1998; Ochsenkuhn et al., 2003; Schieve et al., 2003; Shevell et al., 2005; Tan et al., 1992).

This study observed a 1.72-fold increase in preterm birth among assisted reproduction pregnancies. Similar findings were described in two meta-analyses (Helmerhorst et al., 2004; Jackson et al., 2004). The exact mechanism related to the increased risk for prematurity in singleton assisted reproduction pregnancies remains unclear. Wang et al. (2002) observed a significantly increased 2.4-fold risk for prematurity following assisted reproduction versus spontaneous conception and only a 1.5-fold increased risk following intrauterine insemination, concluding that the increased risk for prematurity may be the result of the modality of treatment.

However, only IVF cycles (but not ICSI) were associated with an almost 2-fold increased risk for prematurity. Infertility diagnosis has been suggested as a possible aetiology for excess of prematurity. The current study observed an increased risk (although not significant) for prematurity in women with female infertility as compared with male factor infertility. Similarly, Wang et al. (2005) and Pinborg et al. (2005) observed a higher rate of prematurity in singletons after vanishing twin as compared with singletons where only one embryo was transferred. However, La Sala et al. (2006), as well as the current study, having an even larger sample size failed to observe this risk. An increased risk for congenital malformations, yet not significant, was evident in the current study among assisted reproduction pregnancies, supporting other reports (Hansen et al., 2002; Kallen et al., 2005a; Katalinic et al., 2004; Klemetti et al., 2005; Rimm et al., 2004; Zhu et al., 2006).

The major strength of this study is the prospective follow up of women who conceived following assisted reproduction treatment with an appropriate control group of women conceiving spontaneously who were followed in the same manner, thus allowing us to evaluate parameters such as spontaneous abortions and pregnancy complications.

Furthermore, the prospective design enabled adjustment for several confounders that are usually limited in registry-based studies, such as previous obstetric history, complications during pregnancy and lifestyle including smoking and BMI. Finally, this study was able to compare and adjust for specific treatment characteristics such as the type and number of embryos transferred.

The limitation of this study is that the study population was recruited from only two medical centres. However, this population is not expected to be selective, since assisted reproduction treatment in Israel is funded by the Ministry of Health for the first and second children with no limitation on the number of cycles.

In conclusion, this study did not show increased risk of pregnancy-associated complications in singleton pregnancies following assisted reproduction as compared with spon-

taneous conception, except for excess of vaginal bleeding. Singleton neonates born following assisted reproduction were, however, at increased risk for preterm delivery. The risk of prematurity and low birthweight occurred in IVF, rather than ICSI, pregnancies.

## Acknowledgement

The study was partially funded by the Israel National Institute for Health Policy and Health Services Research (Grant no. 05/79).

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*Declaration: The authors report no financial or commercial conflicts of interest.*

Received 30 May 2012; refereed 16 January 2013; accepted 17 January 2013.