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# Incidence of spontaneous abortion among pregnancies produced by assisted reproductive technology

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**BACKGROUND: There has been increasing number of pregnancies following assisted reproductive technology treatment and their survival is understandably a matter of interest. The relative risk of spontaneous abortion in these pregnancies remains unclear. The objectives of this study were to quantify the relative risk in assisted reproductive technology pregnancies in relation to two cohorts of naturally conceived pregnancies and to assess the possible risk factors for spontaneous abortion among assisted reproductive technology pregnancies. METHODS: Three cohorts of pregnancies, 1945 pregnancies conceived following assisted reproductive technology treatment in a tertiary infertility clinic, 549 natural pregnancies in a prospective study of lifestyle and pregnancy (the Ford cohort), and 4265 pregnancies from another cohort (the Treloar cohort), were used in the study. RESULTS: After adjusting for age, the relative risk of spontaneous abortion was 1.20 (95% CI 1.03–1.46) in the assisted reproductive technology cohort in comparison with the Ford cohort. Within the assisted reproductive technology cohort, a history of spontaneous abortion predicted increased risk, while a low level of ovarian stimulation seemed to be related to a reduced risk. CONCLUSIONS: The study showed that the risk of spontaneous abortion was slightly increased in the assisted reproductive technology pregnancies after adjusting for maternal age and previous spontaneous abortion. Within the assisted reproductive technology cohort, several variables, including the level of stimulation, appeared to be linked with the risk of spontaneous abortion.**

*Key words*: assisted reproductive technology/infertility/maternal age/ovarian stimulation/spontaneous abortion

## Introduction

In the past two decades, steadily increasing numbers of couples with infertility have been treated by techniques such as IVF, gamete intra-Fallopian transfer (GIFT) or ICSI, collectively known as assisted reproductive technology. These techniques generally involve using gonadotrophins to stimulate the ovary resulting in multiple follicle development, obtaining the mature oocytes surgically, manipulating gametes *in vitro*, and transferring the gametes/embryos into the uterus within 2–3 days (Edwards *et al*., 1980; Edwards and Craft, 1990; Khamsi *et al*., 1998). These methods have produced tens of thousands of conceptions yearly worldwide (Hurst and Lancaster, 2001; Nygren and Andersen, 2001; Anonymous, 2002).

The survival of assisted reproductive technology conceptions is understandably a matter of interest. Even among naturally conceived pregnancies, spontaneous loss is not uncommon. About 10–15% of all natural pregnancies end in recognized spontaneous abortions (Wilcox *et al*., 1981; Risch *et al*., 1988; Nybo Andersen *et al*., 2000; De La Rochebrochard and Thonneau, 2002). Reports from many infertility centres have shown a much higher incidence of spontaneous abortion among assisted reproductive technology pregnancies, in the range of 18–30% (Seppala, 1985; Liu *et al*., 1988; Saunders and Lancaster, 1989; Breart and de Mouzon, 1995; FIVNAT, 1995).

While the risk of spontaneous abortion appears to be higher among assisted reproductive technology pregnancies than that reported in the general population, the comparison can be misleading. Assisted reproductive technology pregnancies are commonly under intense surveillance, so losses from a very early stage of the pregnancy are often carefully documented and reported. In contrast, spontaneous abortion rates among natural conceptions are notoriously difficult to measure and can be easily underestimated by assisted reproductive technology standards. Also women who received assisted reproductive technology treatment are a selected group with characteristics that may predispose them to an increased risk of spontaneous abortion. For example, women who receive assisted reproductive technology treatment tend to be older and have experienced previous spontaneous abortion. These are all known risk factors for spontaneous abortion (Abdalla *et al*., 1993; Weinberg *et al*., 1994; Gray *et al*., 1995; De La

 

**Table I.** Age and other characteristics of women in the cohorts (mean and SD)

| | *n* | Mean age (years) | % >30 years old | % with previous spontaneous abortion | % primparous women |
|---|---|---|---|---|---|
| ART cohort | 1945 | 32.4 (4.0) | 72 | 33 | 66 |
| Ford cohort | 549 | 29.4 (4.2) | 47 | N/A[a] | N/A[a] |

[a]No data are available for the obstetric history of this cohort.
ART = assisted reproductive technology.

Rochebrochard and Thonneau, 2002) and need to be taken into consideration. Two small studies comparing the risk of spontaneous abortion in assisted reproductive technology pregnancies with the risk in natural pregnancies (Steer *et al*., 1989; Pezeshki *et al*., 2000) concluded that there was no increased risk in assisted reproductive technology pregnancies. However, both studies were limited by small size and unclear definitions of pregnancy and spontaneous abortion. One study has suggested an increased risk of spontaneous abortion among assisted reproductive technology pregnancies, but there was no estimation of the excess risk (Ezra and Schenker, 1995). Information about the presence and the extent of excess risk of spontaneous abortion in assisted reproductive technology pregnancies would be useful for assessing the outcomes of assisted reproductive technology treatment and patient counselling. Similarly, knowledge on the risk factors within the assisted reproductive technology cohort can be used for such purposes too.

The main objective of this study was to quantify the risks of spontaneous abortion in a cohort of assisted reproductive technology pregnancies in relation to two cohorts of naturally conceived pregnancies with adjustment for age and previous spontaneous abortion. Another objective was to assess the treatment and population-related risk factors for spontaneous abortion among assisted reproductive technology pregnancies.

## Materials and methods

There were 1698 women who conceived at least one pregnancy following assisted reproductive technology treatment in the Reproductive Medicine Unit, Department of Obstetrics & Gynecology, University of Adelaide, Australia, during the study period of 1982–1996. Altogether they had achieved 1996 pregnancies, including 37 ectopic pregnancies and 14 pregnancies that subsequently underwent induced abortion, which were excluded from the final analysis, so the study population consisted of 1945 pregnancies. The preliminary treatment protocol remained generally stable except for a change in ovarian stimulation in 1988 (Sathanandan *et al*., 1989; Norman *et al*., 1991). The treatment mode was IVF only before 1985, while GIFT was first used in 1985 and ICSI in 1993. Details of these procedures have been reported elsewhere (Kerin *et al*., 1984; Sathanandan *et al*., 1989; Matthews *et al*., 1991; Norman *et al*., 1991; Payne *et al*., 1994). Most couples were fully investigated for infertility aetiology prior to treatment. Forty-five per cent of women were diagnosed with a female infertility factor. Thirty-nine per cent had a husband with semen defects (with or without female factors). Among these, about one-third conceived by donated sperm. The remaining 16% of women had no apparent reason for their infertility. Of the eligible pregnancies, 56% (1097) were produced by IVF, 21% (411) by ICSI and 23% (437) by GIFT. In order to explore whether stimulation of the ovary might also be related to the risk of subsequent loss, the level of estradiol at the time of hCG administration before oocyte retrieval was used as an indicator of the ovarian stimulation level. We have separated the study period into four sub-periods, 1983–1985 (early period of assisted reproductive technology), 1986 to 1988 (before the major stimulation protocol change), 1989–1991 (post-stimulation protocol change), 1992–1996 (stable period).

We sought a comparison group of naturally conceived pregnancies for assessment of their risk of spontaneous abortion. The choice of an appropriate comparison group is problematic. There are few studies in which large numbers of naturally conceived pregnancies have been defined prospectively and with comparably detailed data recorded. We have chosen two studies where pregnancies had been prospectively followed. The primary comparison group was from prospective follow-up of couples ($n = 969$) who were trying to achieve pregnancy. This study was carried out in the same location as the assisted reproductive technology cohort during late 1980 and early 1990 (Ford *et al*., 1994). The original objective of that study was to establish the association between occurrence and outcomes of pregnancy and lifestyle factors. A total of 549 pregnancies established naturally without infertility treatment in this group was included in the study (the Ford cohort).

The second study was designed as a prospective study of menstrual cycles (Treloar *et al*., 1967). This cohort (termed here as the Treloar cohort) of white, college-educated Minnesota women maintained calendars of their menstrual cycles for up to 40 years. In the 4877 pregnancies recorded, we excluded 451 (9.2%) that lacked the date of the last menstrual period (LMP), 80 (1.6%) that did not survive ⩾6 weeks after LMP, 63 (1.3%) that ended in induced abortion, and 18 (0.4%) ectopic pregnancies. We included 4265 intrauterine pregnancies that survived to ⩾6 weeks of gestation in the present study.

In both assisted reproductive technology and Ford cohorts, the pregnancy was first detected by the raised hCG concentration in either serum (assisted reproductive technology cohort) or urine (Ford cohort) at 4–5 weeks of gestation. This was often followed by further ultrasound scan at 6–7 weeks of gestation to confirm the establishment of the pregnancy. In the Treloar cohort, pregnancy was self-reported by subjects who had been routinely monitoring their menstrual cycles. All pregnancies included in this study lasted ⩾6 weeks after the LMP. Spontaneous abortion in the assisted reproductive technology cohort was defined as either a self-reported loss of pregnancy, or the absence of a gestational sac at a subsequent ultrasound scan after the initial detection of pregnancy, or a fetal death detected at a subsequent ultrasound scan 6 weeks after the LMP but before 20 full weeks of gestation. In the natural pregnancy cohorts, spontaneous abortion was defined as a self-reported loss of pregnancy, or a medically confirmed pregnancy loss or fetal death over the same period.

**Table II.** Unadjusted risks of spontaneous abortion for the cohorts stratified by maternal age

| | Age (years) | | | | |
|---|---|---|---|---|---|
| | <25 | 25–29 | 30–34 | 35–39 | ⩾40 |
| ART cohort (%) | 19 (59[a]) | 17 (492) | 18 (899) | 24 (433) | 40 (62) |
| Ford cohort (%) | 23 (68) | 12 (265) | 15 (191) | 25 (57) | 50 (8) |
| RR (95% CI), ART versus Ford | 0.83 (0.42–1.67) | 1.51 (1.01–2.28) | 1.23 (0.85–1.78) | 0.95 (0.60–1.52) | 0.81 (0.34–1.90) |

[a]Values in parentheses represent number of pregnancies in the stratum.
ART = assisted reproductive technology; RR = relative risk; CI = confidence interval.

Differences between the assisted reproductive technology cohort and the control cohorts were assessed either by Student's *t*-test or $\chi^2$-test (Fisher's exact test if the cell number was <5). Adjusted relative risks for spontaneous abortion were calculated by the Cochrane–Mantel–Haenszel method. Multivariate logistic regression analysis was used to assess the risk factors for spontaneous abortion within the assisted reproductive technology cohort.

## Results

### *Risk of spontaneous abortion*

There were 402 spontaneous abortions among the 1945 assisted reproductive technology pregnancies, for an overall loss rate of 21%. Risk in the Ford cohort was 16% (87/549) and 14% in the Treloar cohort (605/4265). The unadjusted relative risk for assisted reproductive technology pregnancies was 1.33 (95% CI 1.08–1.65) in contrast to the Ford cohort and 1.49 (1.33–1.68) in contrast to the Treloar cohort. Women in the assisted reproductive technology cohort were older than those in the control cohorts, more likely to be primparous, and with a greater likelihood of previous spontaneous abortion (Table I).

The relative risk controlling for age, using Cochrane–Mantel–Haenszel method, was 1.20 (1.03–1.46) (assisted reproductive technology cohort versus Ford cohort) and 1.37 (1.22–1.54) (assisted reproductive technology cohort versus Treloar cohort) respectively. Table II shows the risk of spontaneous abortion for the assisted reproductive technology and Ford cohorts, stratified by maternal age. Between 25 and 35 years of age, assisted reproductive technology pregnancies had a higher relative risk of spontaneous abortion, although the excess risk in the higher age group was not significant. Adjusting for both age and the number of previous spontaneous abortions resulted in no further reduction of the relative risk, 1.34 (1.19–1.51) in the assisted reproductive technology cohort versus Treloar cohort.

The overall risk in the first trimester of gestation was 16.5% in the assisted reproductive technology cohort versus 14.0% in the Ford cohort ($P < 0.05$) and 11.3% in the Treloar cohort ($P < 0.01$). There was a significant difference ($P < 0.05$) between the assisted reproductive technology cohort and control cohorts in the risk of spontaneous abortion in the second trimester of gestation, 4.5% in the assisted reproductive technology cohort, 2.0% in the Ford cohort and 2.7% in the Treloar cohort.

### *Risk factors for spontaneous abortion in the assisted reproductive technology cohort*

The persistence of an excess risk among assisted reproductive technology pregnancies, even after controlling for maternal age and previous spontaneous abortion, suggests possible effects of the assisted reproductive technology population characteristics or treatment itself. In order to pursue this question, we assessed the risk of spontaneous abortion within sub-groups of assisted reproductive technology pregnancies based on various risk factors. Table III shows the risk of spontaneous abortion within each sub-group and the odds ratios adjusted for other factors. The odds ratios were calculated from the multivariate logistic regression analysis including age, BMI and all other factors in the table.

Risk of spontaneous abortion was positively and significantly related to the woman's age and a history of spontaneous abortion. However, it did not vary by the aetiology of infertility. The risk differed between the treatment options with the highest risk seen among women treated by IVF, and the lowest risk in those treated by GIFT. After adjustment for age and other factors, the difference between IVF and GIFT pregnancies remained statistically significant. There was a significant trend effect from very low level of stimulation to the highest level of stimulation ($P < 0.01$). There was, however, no significant trend across the time period of treatment ($P = 0.56$).

## Discussion

We found a small excess risk of spontaneous abortion among assisted reproductive technology pregnancies after adjusting for maternal age. Adjusting for previous spontaneous abortion and material age caused a slight reduction in risk. The excess of risk occurred in both the first and second trimester of the gestation in the assisted reproductive technology cohort. A small disparity was found within the assisted reproductive technology cohort in terms of the risk of spontaneous abortion between the treatments and ovarian stimulation levels, whereas no difference was found between the types of patients or early and more recent patients.

Several previous studies have compared the risk of spontaneous abortion following assisted reproductive technology with that in natural pregnancies. Typically, these studies have not clearly stated the definitions of pregnancy and spontaneous abortion (Steer *et al*., 1989; Ezra and Schenker, 1995; Pezeshki *et al*., 2000). While it would be ideal, it is logistically difficult to conduct a prospective study that directly follows both

**Table III.** The percentage of spontaneous abortion and adjusted odds ratio (OR) by treatment and other characteristics of women conceiving by assisted reproductive technology

| | *n* | Spontaneous abortion (%) | OR | 95% CI | *P* |
|---|---|---|---|---|---|
| Age (years) | | | | | |
| <25 | 58 | 20 | 1.00 | | |
| 25–29.9 | 487 | 20 | 0.90 | 0.45–1.81 | 0.56 |
| 30–34.9 | 898 | 19 | 0.87 | 0.44–1.71 | 0.45 |
| 35–39.9 | 439 | 25 | 1.22 | 0.60–2.45 | 0.77 |
| ⩾40 | 63 | 38 | 2.42 | 1.01–5.78 | 0.03 |
| Previous spontaneous abortion | | | | | |
| None | 1312 | 20 | 1.00 | | |
| 1 | 471 | 21 | 1.00 | 0.75–1.32 | 0.23 |
| 2 | 117 | 26 | 1.15 | 0.71–1.85 | 0.31 |
| ⩾3 | 45 | 34 | 2.09 | 1.07–4.10 | 0.02 |
| Patient type | | | | | |
| Female single factor | 638 | 21 | 1.00 | | |
| Female multiple factors | 211 | 21 | 1.01 | 0.67–1.52 | 0.39 |
| Male factor/donor sperm | 260 | 18 | 0.90 | 0.57–1.42 | 0.38 |
| Male factor/ICSI | 205 | 22 | 1.14 | 0.59–2.20 | 0.56 |
| Male factor/IVF or GIFT | 250 | 22 | 1.19 | 0.76–1.84 | 0.42 |
| Unexplained | 280 | 24 | 1.22 | 0.85–1.75 | 0.39 |
| Others | 101 | 17 | 0.92 | 0.49–1.71 | 0.40 |
| Treatment | | | | | |
| IVF | 1093 | 23 | 1.00 | | |
| ICSI | 413 | 20 | 0.91 | 0.54–1.54 | 0.36 |
| GIFT | 439 | 18 | 0.74 | 0.34–0.99 | 0.04 |
| Levels of estradiol at hCG | | | | | |
| <2 nmol/l | 42 | 10 | 1.00 | | |
| 2–8 nmol/l | 1070 | 20 | 2.06 | 0.76–5.56 | 0.67 |
| >8 nmol/l | 833 | 23 | 2.59 | 0.96–6.99 | 0.72 |
| Sub-period | | | | | |
| 1983–1985 | 114 | 20 | 1.00 | | |
| 1986–1988 | 350 | 18 | 0.95 | 0.51–1.74 | 0.40 |
| 1989–1991 | 414 | 21 | 1.12 | 0.61–2.05 | 0.51 |
| 1992–1996 | 1067 | 22 | 1.13 | 0.67–1.95 | 0.50 |

CI = confidence interval; GIFT = gamete intra-Fallopian transfer.

naturally conceived and assisted reproductive technology treatment pregnancies using uniform methods of surveillance. In the present study, we have obtained two independent cohorts of naturally conceived pregnancies, both prospectively followed up with detailed data on date of LMP and the gestational week of the spontaneous abortion. This makes the definition of pregnancy and spontaneous abortion as comparable as possible. It is an advantage that the Ford cohort was a prospective study of pregnancy in women who were seeking to achieve pregnancy with their pregnancy determined by urine hCG and ultrasound under a protocol nearly as rigorous as for the assisted reproductive technology cohort. In addition it was followed up during a similar time in the same location as the assisted reproductive technology cohort, therefore it may be more comparable with the assisted reproductive technology cohort and used as the primary comparison cohort. The Treloar cohort was from another continent over a different time period with different detection method for pregnancy, so it is a much weaker comparison group. Its strengths include the precise information on gestational age, the availability of some obstetric history and the large sample size. While the Treloar data cover several decades, there is no evidence that the risk of spontaneous abortion has changed in this cohort over time (Wilcox *et al*., 1981).

Spontaneous abortion is more common in older women (Wilcox *et al*., 1981; Nybo Andersen *et al*., 2000). It is also well known that women with previous spontaneous abortion have an increased risk of spontaneous abortion (Nybo Andersen *et al*., 2000). Therefore, adjustment for such risk factors is essential for a reliable estimate of the excess risk in assisted reproductive technology pregnancies in comparison with natural pregnancies. Adjusting for these risk factors reduced the excess risk in assisted reproductive technology pregnancies but did not eliminate it. Most women in all three cohorts were English-speaking women of European ancestry and with average or above average education. One well-recognized characteristic of assisted reproductive technology pregnancies is its high prevalence of multiple pregnancies which are routinely detected by ultrasound in early pregnancy. Few data on early detection of multiple pregnancy are available in the natural pregnancies although the prevalence of multiple pregnancy is low judged on the birth outcome. The rates of pregnancy loss were shown to be similar for multiple implantations compared with single implantation in an oocyte donor programme (Legro *et al*., 1995). There were also reports of reduced risk of spontaneous abortion in women with multiple pregnancy (Schieve *et al*., 2003; Tummers *et al*., 2003) and this is likely due to the masking effect of the remaining developing fetus in assisted reproductive technology multiple pregnancies (Kol *et al*., 1993; Rodriguez-Gonzalez *et al*., 2002). Indeed, these results suggested that the observed risk of spontaneous abortion in the assisted reproductive technology cohort might have been

reduced by inclusion of multiple pregnancies. Finally, the effect of other confounding factors cannot be adjusted for in this study due to the lack of data.

An important weakness of the Treloar cohort is its dependence on self-reported pregnancy and pregnancy loss. A false-positive error could occur if a prolonged menses, i.e. longer than unusual and 6 weeks after the LMP) was mistakenly identified by the woman as a spontaneous abortion. False-negative errors would occur when an actual loss, again later than 6 weeks after the LMP with the usual period of similar length, was mistakenly interpreted as a late period. Though we cannot rule out either type of error, the incidence may not be great since these women had been carefully recording, and should be familiar with, their menstrual cycles. Also, the distorting influence of these errors would be strongest during the very early stage of pregnancy, and would be smaller by 6 weeks from LMP and thereafter. In this regard, the Ford cohort may have served as a better control. Another possible difference between the cohorts is the completeness of data on previous spontaneous abortion, although this may not differ greatly between the assisted reproductive technology and Treloar cohorts. We cannot exclude the possibility that some patients in the Treloar cohort were treated for infertility, although the chance was very small since the last pregnancy in that cohort occurred in the early 1980s when assisted reproductive technology was only used on very small scale in USA.

The study cannot distinguish whether the increased risk of spontaneous abortion in assisted reproductive technology pregnancies is due to the treatment they received, or to unmeasured patient characteristics. Population differences, such as maternal age and previous spontaneous abortion, certainly accounted for part of the increased risk. Women with a history of infertility have been reported to have higher rates of spontaneous abortion (Barton, 1968; Risch *et al*., 1988). In one study which failed to detect the difference in the risk of spontaneous abortion between assisted reproductive technology pregnancies and natural pregnancies, the natural pregnancies in fact occurred in women with an infertility history (Pezeshki *et al*., 2000), suggesting that the lack of difference may be due to the similarity in the background of the women. In deed, Gray and Wu (2000) have reported a significantly higher risk of spontaneous abortion in women with a history of subfertility. There were also reports of higher rates of other reproductive problems such as very low birthweight and perinatal mortality (Venn and Lumley, 1993) and preterm delivery (Henriksen *et al*., 1997) in women with an infertility history. Thus, it is possible that infertility problems may predispose the women to an increased risk for reproductive problems, including spontaneous abortion as suggested by Baird *et al*. (1999) that an exposure first causes infertility, then jeopardizes the pregnancy once conception occurs.

Within the assisted reproductive technology cohort, there was some disparity in terms of abortion risk between various subgroups. The pregnancies conceived following GIFT had a lower risk of spontaneous abortion than those by IVF/ICSI. Although the actual cause of this is not clear, this may be due to the more natural fertilization and development of the embryo in GIFT treatment and/or the characteristics of this group of patients. Furthermore, there was indication of an association between the risk of spontaneous abortion and the level of ovarian stimulation. A previous report showed that there was an increased risk of abortion in IVF patients with severe ovarian hyperstimulation syndrome (Raziel *et al*., 2002). Of course, the levels of stimulation, as assessed by $E_2$ concentrations, in most assisted reproductive technology cycles here were not as high as in hyperstimulation syndrome but much higher than natural cycles. Finally, although there have been many changes or innovations introduced in assisted reproductive technology treatment processes over the study period, little change or trend across the period of the study was found.

Spontaneous abortion can be attributed to several factors involved in human reproduction, including genetic and uterine abnormalities, endocrine and immunological dysfunctions, infectious agents, environmental pollutants, psychogenetic factors and endometriosis, as summarized by Bulletti *et al*. (1996). In the assisted reproductive technology cohort, genetic defects, possibly due to the lack of gamete selection (Koulischer *et al*., 1997), endometriosis (Dicker *et al*., 1992), obesity and high serum insulin concentration (Hamilton-Fairley *et al*., 1992; Craig *et al*., 2002; Wang *et al*., 2002) and possibly hypersecretion of LH (van Hooff *et al*., 1994) all can be responsible for the higher risk of spontaneous abortion. Since the excess of risk occurred in both the first and second trimester, it also indicates that there may be multiple causes for the increased risk.

In conclusion, the results of this study suggest that the risk of spontaneous abortion may be increased by ~20–34% in this cohort of assisted reproductive technology pregnancies than in the natural pregnancies after adjusting for differences in maternal age and previous spontaneous abortion. It is important for patients to know that there is such a risk even though it may be acceptable to them. Within the assisted reproductive technology cohort, it appears that by far the most important factor predicting the risk of spontaneous abortion is previous spontaneous abortion, while some treatment related factors may also be linked with increased risk. Further studies are needed to confirm the possible effect of some treatment-related factors.

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## References

Abdalla HI, Burton G, Kirkland A, Johnson MR, Leonard T, Brooks AA and Studd JW (1993) Age, pregnancy and miscarriage: uterine versus ovarian factors. Hum Reprod 8,1512–1517.

Anonymous (2002) Assisted reproductive technology in the United States: 1998 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. Fertil Steril 77,18–31.

Baird DD, Wilcox AJ and Kramer MS (1999) Why might infertile couples have problem pregnancies? [comment]. Lancet 353,1724–1725.

Barton M (1968) Fertility in married women. J Reprod Fertil 16,327–331.

Breart G and de Mouzon J (1995) [Assisted reproduction vigilance]. Bull Acad Natl Med 179,1759–1764.

Bulletti C, Flamigni C and Giacomucci E (1996) Reproductive failure due to spontaneous abortion and recurrent miscarriage. Hum Reprod Update 2,118–136.

Craig L, Ke R and Kutteh W (2002) Increased prevalence of insulin resistance in women with a history of recurrent pregnancy loss. Fertil Steril 78,487.

De La Rochebrochard E and Thonneau P (2002) Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. Hum Reprod 17,1649–1656.

Dicker D, Goldman JA, Levy T, Feldberg D and Ashkenazi J (1992) The impact of long-term gonadotropin-releasing hormone analogue treatment on preclinical abortions in patients with severe endometriosis undergoing in vitro fertilization–embryo transfer. Fertil Steril 57,597–600.

Edwards RG and Craft I (1990) Development of assisted conception. Br Med Bull 46,565–579.

Edwards RG, Steptoe PC and Purdy JM (1980) Establishing full-term human pregnancies using cleaving embryos grown in vitro. Br J Obstet Gynecol 87,737–756.

Ezra Y and Schenker JG (1995) Abortion rate in assisted reproduction—true increase? Early Pregn 1,171–175.

FIVNAT (French In Vitro National) (1995) Pregnancies and births resulting from in vitro fertilization: French national registry, analysis of data 1986 to 1990. Fertil Steril 64,746–756.

Ford JH, MacCormac L and Hiller J (1994) PALS (pregnancy and lifestyle study): association between occupational and environmental exposure to chemicals and reproductive outcome. Mutat Res 313,153–164.

Gray RH and Wu LY (2000) Subfertility and risk of spontaneous abortion. Am J Publ Health 90,1452–1454.

Gray RH, Simpson JL, Kambic RT, Queenan JT, Mena P, Perez A and Barbato M (1995) Timing of conception and the risk of spontaneous abortion among pregnancies occurring during the use of natural family planning. Am J Obstet Gynecol 172,1567–1572.

Hamilton-Fairley D, Kiddy D, Watson H, Paterson C and Franks S (1992) Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin. Br J Obstet Gynecol 99,128–131.

Henriksen TB, Baird DD, Olsen J, Hedegaard M, Secher NJ and Wilcox AJ (1997) Time to pregnancy and preterm delivery. Obstet Gynecol 89,594–599.

Hurst T and Lancaster P (2001) Assisted Conception Australia and New Zealand 1999 and 2000. AIHW cat. no. PER 18. Sydney: Australian Institute of Health and Welfare National Perinatal Statistics Unit. (Assisted Conception Series no. 6.)

Kerin JF, Warnes GM, Quinn P, Kirby C, Jeffrey R, Matthews CD, Seamark RF, Texler K, Antonas B and Cox LW (1984) In vitro fertilization and embryo transfer program, Department of Obstetrics and Gynecology, University of Adelaide at the Queen Elizabeth Hospital, Woodville, South Australia. J In Vitro Fertil Embryo Transfer 1,63–71.

Khamsi F, Lacanna I, Endman M and Wong J (1998) Recent advances in assisted reproductive technologies. Endocrine 9,15–25.

Kol S, Levron J, Lewit N, Drugan A and Itskovitz-Eldor J (1993) The natural history of multiple pregnancies after assisted reproduction: is spontaneous fetal demise a clinically significant phenomenon? Fertil Steril 60,127–130.

Koulischer L, Verloes A, Lesenfants S, Jamar M and Herens C (1997) Genetic risk in natural and medically assisted procreation. Early Pregn 3,164–171.

Legro RS, Wong IL, Paulson RJ, Lobo RA and Sauer MV (1995) Multiple implantation after oocyte donation: a frequent but inefficient event. Fertil Steril 63,849–853.

Liu HC, Jones GS, Jones HW Jr and Rosenwaks Z (1988) Mechanisms and factors of early pregnancy wastage in in vitro fertilization–embryo transfer patients. Fertil Steril 50,95–101.

Matthews CD, Warnes GM, Norman RJ, Phillipson G, Kirby CA and Wang X (1991) The leuprolide flare regime for in-vitro fertilization/gamete intrafallopian transfer and embryo cryopreservation. Hum Reprod 6,817–822.

Norman RJ, Warnes GM, Wang X, Kirby CA and Matthews CD (1991) Differential effects of gonadotrophin-releasing hormone agonists administered as desensitizing or flare protocols on hormonal function in the luteal phase of hyperstimulated cycles. Hum Reprod 6, 206–213.

Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J and Melbye M (2000) Maternal age and fetal loss: population based register linkage study. Br Med J 320,1708–1712.

Nygren KG and Andersen AN (2001) Assisted reproductive technology in Europe, 1998. Results generated from European registers by ESHRE. European Society of Human Reproduction and Embryology. Hum Reprod 16,2459–2471.

Payne D, Flaherty SP, Jeffrey R, Warnes GM and Matthews CD (1994) Successful treatment of severe male factor infertility in 100 consecutive cycles using intracytoplasmic sperm injection. Hum Reprod 9,2051–2057.

Pezeshki K, Feldman J, Stein DE, Lobel SM and Grazi RV (2000) Bleeding and spontaneous abortion after therapy for infertility. Fertil Steril 74,504–508.

Raziel A, Friedler S, Schachter M, Strassburger D, Mordechai E and Ron-El R (2002) Increased early pregnancy loss in IVF patients with severe ovarian hyperstimulation syndrome. Hum Reprod 17,107–110.

Risch HA, Weiss NS, Clarke EA and Miller AB (1988) Risk factors for spontaneous abortion and its recurrence [see comments]. Am J Epidemiol 128,420–430.

Rodriguez-Gonzalez M, Serra V, Garcia-Velasco JA, Pellicer A and Remohi J (2002) The 'vanishing embryo' phenomenon in an oocyte donation programme. Hum Reprod 17,798–802.

Sathanandan M, Warnes GM, Kirby CA, Petrucco OM and Matthews CD (1989) Adjuvant leuprolide in normal, abnormal and poor responders to controlled ovarian hyperstimulation for in vitro fertilization/gamete intrafallopian transfer. Fertil Steril 51,998–1006.

Saunders DM and Lancaster P (1989) The wider perinatal significance of the Australian in vitro fertilization data collection program. Am J Perinatol 6,252–257.

Schieve, LA, Tatham L, Peterson HB, Toner J and Jeng G (2003) Spontaneous abortion among pregnancies conceived using assisted reproductive technology in the United States. Obstet Gynecol 101,959–967.

Seppala M (1985) The world collaborative report on in vitro fertilization and embryo replacement: current state of the art in January 1984. Ann NY Acad Sci 442,558–563.

Steer C, Campbell S, Davies M, Mason B and Collins W (1989) Spontaneous abortion rates after natural and assisted conception. Br Med J 299,1317–1318.

Treloar AE, Boynton RE, Behn BG et al (1967) Variation of the human menstrual cycle through reproductive life. Int J Fertil 12, 77–126.

Tummers P, De Sutter P and Dhont M (2003) Risk of spontaneous abortion in singleton and twin pregnancies after IVF/ICSI. Hum Reprod 18,1720–1723.

van Hooff M, Schoute E and Schoemaker J (1994) Hypersecretion of luteinizing hormone (LH) and ovarian steroids in women with recurrent abortion [letter; comment]. Hum Reprod 9,179–180.

Venn A and Lumley J (1993) Births after a period of infertility in Victorian women 1982–1990. Aust NZ J Obstet Gynecol 33, 379–384.

Wang JX, Davies MJ and Norman RJ (2002) Obesity increases the risk of spontaneous abortion during infertility treatment. Obes Res 10,551–554.

Weinberg CR, Baird DD and Wilcox AJ (1994) Bias in retrospective studies of spontaneous abortion based on the outcome of the most recent pregnancy. Ann NY Acad Sci 709,280–286.

Wilcox AJ, Treloar AE and Sandler DP (1981) Spontaneous abortion over time: Comparing occurrence in two cohorts of women a generation apart. Am J Epidemiol 114,548–553.

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