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Publication date
2013

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Citation for published version (APA):
van Rumste, M. M. E. (2013). *Outcome measures in reproductive medicine trials*. [Thesis, fully internal, Universiteit van Amsterdam].

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Chapter 6

Interventions and multiple pregnancies in reproductive medicine: critical appraisal of the available evidence

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Submitted

ABSTRACT

OBJECTIVE To assess whether studies evaluating strategies to reduce multiple pregnancies associated with assisted reproductive technologies have sufficient power to detect a clinically meaningful magnitude of effect.

DESIGN Review.

SETTING Randomised controlled trials (RCTs) from the Cochrane Menstrual Disorders and Subfertility Group which have reported on multiple pregnancies.

POPULATION Subfertile couples.

METHODS Data on sample size, power calculation and multiple pregnancies were extracted. For each study, we calculated the sample size required to detect a 50% reduction in the number of multiple pregnancies with 80% power at the 95% confidence level.

MAIN OUTCOME MEASURES Data on multiple pregnancies.

RESULTS We found 83 reviews based on 904 RCTs reporting on pregnancy after fertility treatment. Ten reviews, including 95 RCTs evaluated interventions that aimed to prevent multiple pregnancies. Of these, 9 (9.5%) had sufficient power to detect a minimally important difference in multiple pregnancy rates. Of the remaining 73 reviews, including 809 RCTs with multiple pregnancy as secondary outcome, 176 reported on the numbers of multiple pregnancies (22%). Only 15 (8.5%) of these 176 RCTs had adequate power to detect the imputed minimally important difference for multiple pregnancies.

CONCLUSIONS In reproductive medicine, the overwhelming majority of published clinical studies reporting on interventions aimed at preventing multiple pregnancies lack adequate power. The shift in practice towards strategies aimed at reducing multiple pregnancies is based on intuition rather than robust evaluative data.

INTRODUCTION

Multiple pregnancies are associated with increased risks for both mother and offspring. Women carrying a multiple pregnancy are more susceptible to ante- or postpartum complications, such as anaemia (27%), pre-eclampsia (12%), or labour complications requiring caesarean section. Children born from multiple pregnancies have a more than 50% chance of growth restriction or prematurity (The ESHRE Capri Workshop Group, 2000; Campbell and Templeton, 2004).

Nowadays, more than half of all multiple pregnancies are the result of assisted reproduction techniques (ART), mainly due to ovarian hyperstimulation and transfer of multiple embryos in in-vitro fertilization (IVF) (Fauser *et al.*, 2005). An ESHRE consensus report on the risks and complications in ART concluded that the primary outcome measure in all fertility studies should ideally be singleton live birth rate and that twin and higher order multiple pregnancies should be considered complications (Land and Evers, 2003). In view of this, the European and American Societies for Reproductive Medicine (ESHRE and ASRM) have asked their members to design studies to prevent iatrogenic multiple pregnancies.

It is questionable, however, whether it is at all possible to design and conduct high quality pragmatic RCTs to evaluate the impact of prevention strategies to reduce multiple pregnancies after ART with singleton live birth rate as a primary outcome, as approximately 50% of all multiple pregnancies deliver at or close to term and neonatal survival of prematurely born neonates has improved significantly in recent decades. Detection of differences in health outcomes of multiples versus singletons is becoming increasingly more difficult because of small effect sizes, which require very large numbers of randomised women and a substantially longer follow-up period, which imposes considerable logistical and financial demands on trials. In absence of such RCTs or other comparative studies, the current move towards reduction of multiples runs the risk of being based on intuition rather than on evidence. Obviously, the most effective way to prevent multiple pregnancies caused by ART is to stop offering fertility treatment involving ovarian stimulation, thus bringing multiple pregnancy rates back to the levels experienced in nature. Consequently, reducing the multiple pregnancy rates should always be balanced against a potential decrease in the overall chances of conception.

We asked ourselves whether published fertility studies reporting data on multiple pregnancies had sufficient power to detect a minimally important clinical reduction of 50% in the multiple pregnancy rate. We studied Cochrane Reviews from the Menstrual Disorders and Subfertility Group, which represent the most robust aggregation of trials in reproductive medicine (Windsor *et al.*, 2012). We also scrutinized definitions and analysed data, which presented multiple pregnancy as an outcome.

MATERIALS AND METHODS

The database of the Cochrane Menstrual Disorders and Subfertility Group (MDSG) was searched from inception until September 2012 for the retrieval of reviews of RCTs designed to prevent multiple pregnancies. The reviews were separated into the following treatment categories: ovulation induction (OI), intra-uterine insemination (IUI) with and without ovarian stimulation, in vitro fertilisation (IVF) (including IVF-ICSI) and non-ART. The number of randomised controlled trials (RCTs) reporting on multiple pregnancies within these reviews was listed.

Data from the original publications of the retrieved RCTs were extracted. When the original publication could not be obtained, data were extracted from the Cochrane Review. It was examined whether the RCTs had adequate power to detect a significant difference in multiple pregnancy rates by calculating odds ratios and 95% confidence intervals.

Secondly, all remaining reviews with RCTs on fertility studies (ART or non-ART) within the MDSG were included. These reviews were also categorized as stated above. The number of randomised controlled trials (RCTs) within these reviews mentioning multiple pregnancies was reported. If an RCT was referred to in more than one review, it was only included once. The original publications of the retrieved RCTs were carefully read, and data on the number of multiple pregnancies were extracted. We noted whether a power analysis was performed for multiple pregnancies, and calculated what the required sample-size would have been for a study to have 80% power at the 95% confidence level to detect a 50% reduction in multiple pregnancy rates in the intervention group, which we considered to be the minimally important clinical difference. For each study, we compared the required sample size to the reported sample size. In fertility trials involving comparison of two treatments we were guided by the Cochrane reviews in terms of describing a therapy as an 'intervention' or 'control'.

Subsequently, stratification of the studies on year of publication, i.e. before or after 2003, was performed to determine whether the method of reporting on multiple pregnancies changed after the ESHRE consensus report.

RESULTS

The MDSG contained 178 Cochrane Reviews, of which 16 had been withdrawn (figure 1). Among the 162 active reviews, 83 summarized and appraised topics in the field of reproductive medicine while the other 79 reviews reported on gynaecological topics.

Ten reviews specifically targeted the issue of prevention of multiple pregnancies (figure 1). In two of those reviews no RCTs were included. The other eight reviews included 95 RCTs. In 44 RCTs (46.3%) multiple pregnancies were an outcome measure.

We found 73 reviews on fertility, including RCTs that were not specifically designed to prevent multiple pregnancies, but had multiple pregnancy as a secondary outcome. In 4 of those reviews no RCTs were included. The other 69 reviews included 809 RCTs. In 176 (22%) of these RCTs multiple pregnancies were reported (figure 1).

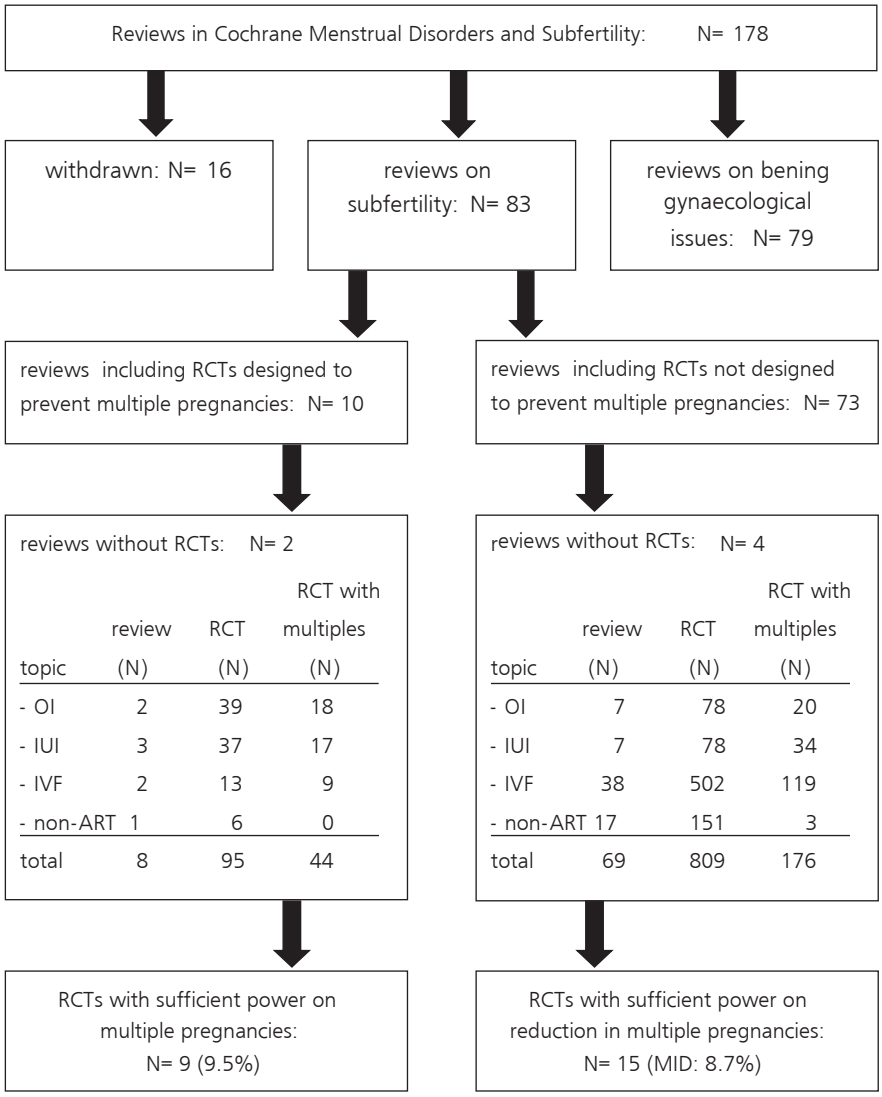

Figure 1. Flow chart of included studies

RCTs intending to prevent multiple pregnancies

The RCTs from the 10 reviews, which studied interventions aimed at preventing multiple pregnancies are categorised in Table 1. None of the included RCTs performed a power analysis on multiple pregnancies to determine the sample size of the study.
Thirty-nine studies on OI were included. In 18 RCTs multiple pregnancies were described. Only one study showed a significant difference in multiple pregnancies between the compared strategies (i.e. the 95% confidence interval did not include 1) (Bayram *et al*., 2004).

Table 1. Randomised controlled trials testing strategies to prevent multiple pregnancies.

treatment strategie review	included RCTs (N)	RCTs including multiple pregnancies (N)	RCTs with significant difference in MPR (N)
Ovulation Induction			
Gonadotrophin therapy for ovulation induction in subfertility associated with polycycstic ovary syndrome	14	6	0
Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome	25	12	1
Intra Uterine Insemination			
Intra-uterine insemination for male subfertility	17	7	2
Intra-uterine insemination for unexplained subfertility	14	9	2
Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples	6	1	0
In Vitro Fertilisation			
In vitro fertilisation for unexplained subfertility	6	2	0
Number of embryos for transfer following in-vitro fertilisation or intra-cytoplasmic sperm injection	7	7	4
In vitro fertilisation versus tubal reanastomosis (sterilisation reversal) for subfertility after tubal sterilization	0	-	-
Surgery for tubal infertility	0	-	-
Non-ART			
Lifestyle changes in women with polycystic ovary syndrome	6	0	0

MPR: multiple pregnancy rate
RCTs: randomised controlled trials

Out of 37 studies on IUI, 17 mentioned multiple pregnancies, of which four (11%) showed significant differences for multiple pregnancies between the treatment strategies.
We found that 9 out of 13 studies on IVF included multiple pregnancy as an outcome. In one review, titled "Number of embryos for transfer following in-vitro fertilisation or

intra-cytoplasmic sperm injection", all included RCTs reported on multiple pregnancies (N=7). Four of the RCTs from this review showed statistically significant differences on multiple pregnancies (31%).
None of the 6 RCTs on non-ART topics mentioned multiple pregnancies. In total, nine of the 95 RCTs showed a significant difference in the multiple pregnancy rate per pregnancy (9.5%).

RCTs where the primary intention was not to test interventions for the prevention of multiple pregnancies

The 809 RCTs on fertility topics that included multiple pregnancies as secondary outcome are described below per category, OI, IUI, IVF and non-ART, respectively. The minimally important clinical difference was calculated per category and is shown in figures.
Seventy-eight studies on ovulation induction were included, of which 20 reported on multiple pregnancies. In four studies the actual number of multiple pregnancies was not reported. In five studies the number of multiple pregnancies in the intervention group was zero and therefore a reduction in multiple pregnancies could not be calculated. None of the remaining 11 studies had enough pregnancies within the study to show a 50% reduction in multiple pregnancies in the intervention group (figure 2).

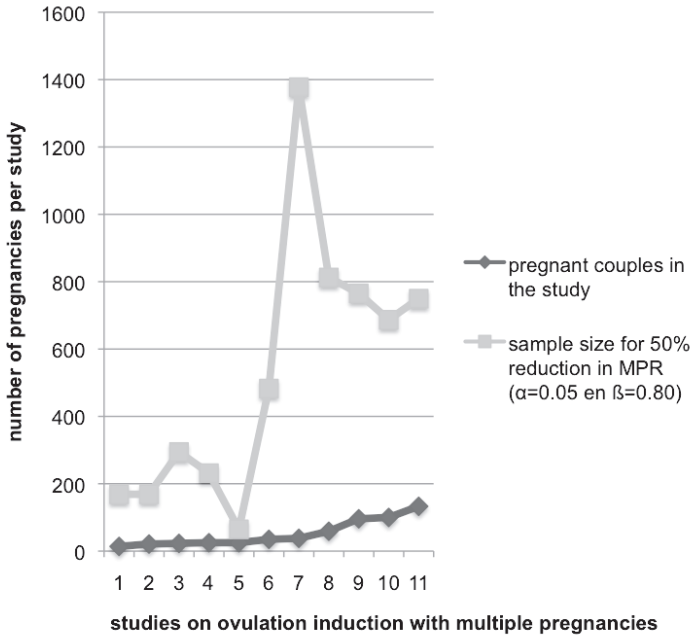

Figure 2. Studies on ovulation induction reporting the number of multiple pregnancies and their number of pregnancies needed in the study to show a reduction in multiple pregnancies by half.

We found 78 studies on IUI, of which 34 mentioned multiple pregnancies in their methods section. In two of these studies, the actual number of multiple pregnancies was not reported. In five studies the number of multiple pregnancies in the intervention group was zero and therefore a reduction in multiple pregnancies could not be calculated. The remaining 27 studies did not have enough pregnancies per study to show a 50% reduction in multiple pregnancies in the intervention group (figure 3).

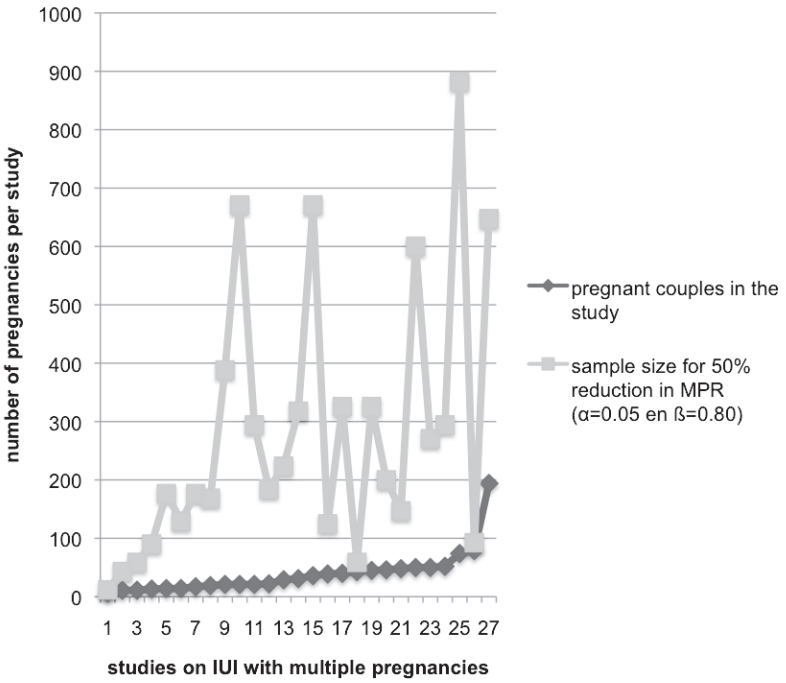

Figure 3. Studies on IUI reporting the number of multiple pregnancies and their number of pregnancies needed in the study to show a reduction in multiple pregnancies by half.

Of the 151 studies on IVF, 119 included multiple pregnancy as an outcome. Twenty did not report on the actual number of multiple pregnancies. In four studies the number of multiple pregnancies in the intervention group was zero and therefore a reduction in multiple pregnancies could not be calculated. Of the remaining 95 studies, 15 (16%) had a sample size large enough to show a reduction in multiple pregnancies in the intervention group by half (figure 4). The topics of these 15 IVF studies were stimulation protocol (N= 3), endometrial preparation prior to embryo transfer (N=1), assisted hatching (N=2), culture media (N=2), timing of embryo transfer (N=3), method of embryo transfer (N=2) and luteal phase interventions (N=3). In these studies the average clinical pregnancy rate was 41% (variation from 22% to 68%). The average multiple pregnancy rate was 35% (variation from 11% to 59%).

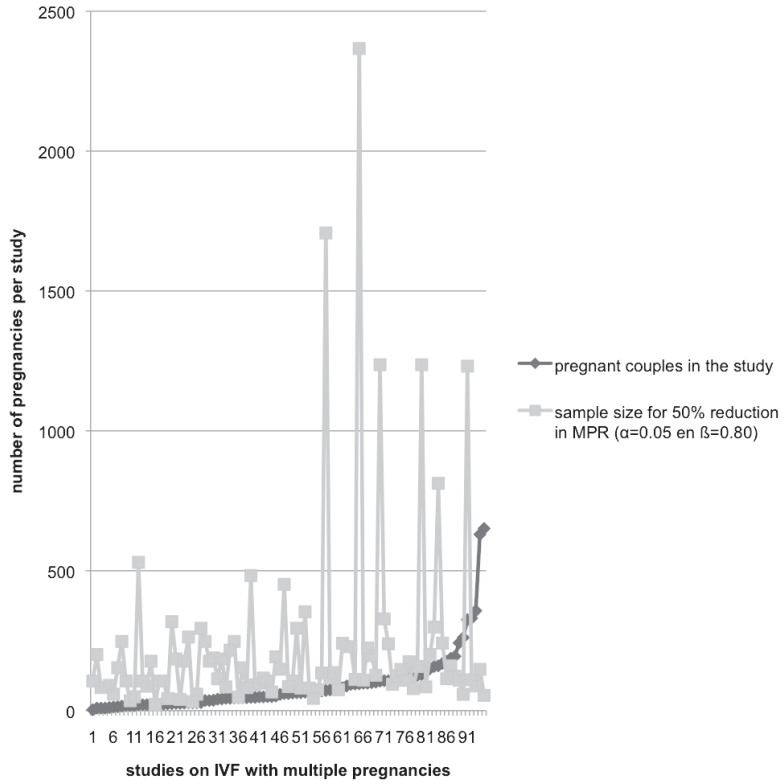

Figure 4. Studies on IVF reporting the number of multiple pregnancies and their number of pregnancies needed in the study to show a reduction in multiple pregnancies by half.

Only three studies on non-ART topics mentioned multiple pregnancies. No analysis was performed on these RCTs, as the three could not be grouped together as they addressed different topics (Chinese herbal medicine for polycystic ovarian syndrome; postoperative procedures following pelvic reproductive surgery; tubal flushing for subfertility).

Minimally important clinical difference

In total, 15 of the 176 (8.5%) analysed RCTs had sufficient power to prove a reduction of 50% in multiple pregnancies.

Power to detect impact on multiple pregnancy rates

Only one of the 904 included RCTs had multiple pregnancy as the primary outcome and performed a power calculation based on this outcome (Frattarelli *et al.*, 2003). This RCT dealt with cleavage stage versus blastocyst stage embryo transfer and was included in the 'RCTs not designed to prevent multiple pregnancies' section. In this study, it was calculated that the required sample-size needed to be136 patients in order to provide 80% chance

of detecting a 25% difference in multiple pregnancy rates, controlling for the probability of type 1 error at alpha = 0.05. Unfortunately, only 49 patients could be included. The minimally important clinical difference was not reached. A sample size of 32 would be necessary, but only 28 couples in the strategy group were pregnant.

Publication year and definitions

Of the 904 included RCTs, 524 were published before 2004. One hundred twenty reported multiple pregnancies (23%). Of the remaining 380 RCTs published in the period since 2004, 96 reported on multiple pregnancies (27%). The outcome multiple pregnancy was often descriptive. For example, it was reported that 'one of the miscarriages was a triplet at 10 weeks and the twins delivered' or 'one quintuplet was reduced to twins, both were live births'. Of most multiple pregnancies the actual outcome was not mentioned, like preterm birth or live birth at a given gestation, but they were only reported as an ongoing pregnancy.

DISCUSSION

Main findings

We evaluated 83 systematic reviews of RCTs of interventions to prevent multiple pregnancy after fertility treatment or with multiple pregnancy as a secondary outcome. Ten reviews reported on a strategy to prevent multiple pregnancy and included 95 RCTs of which 9 RCTs had sufficient power to show a reduction in multiple pregnancies (9.5%).
Of the remaining 73 reviews, which included 809 RCTs with multiple pregnancy as a secondary outcome, 176 reported on the number of multiple pregnancies (22%) and in 173 The minimally important clinical difference was calculated. Only 15 of the analysed RCTs were able to demonstrate a reduction of 50% in multiple pregnancies in the intervention group (8.7%).

Strengths and Limitations

This is the first study to critically appraise the reporting of multiple pregnancy rates in ART studies. Since the number of studies reporting data on multiple pregnancies is limited and only a minority of studies have adequate power to detect a clinically important reduction in multiple pregnancies, it is almost impossible to draw a solid evidence- based conclusion on effective preventive strategies.
We realize that the use of Cochrane MDSG reviews to select RCTs constitutes a selection bias. We preferred to use this search strategy because the reviews included in the MDSG contain only good quality RCTs that are updated on a regular basis and have been critically appraised in a consistent manner. We are reasonably confident that the validity of the

results and conclusions of our current review are not compromised by the selection bias (Windsor *et al.*, 2012).

Apart from the issue of power, which is the topic of this paper, there are also additional factors that hamper any attempt at objective comparison of studies. Not only do outcome measures vary from study to study, but the population included might not be representative for the general population. Usually, young women with a relatively good prognosis are included in fertility trials. Studies also vary in terms of treatment strategies, including drugs used, ovarian stimulation protocols, criteria for cancellation or definition of ovarian hyperstimulation. For example, some clinicians will aim for one dominant follicle in subfertile couples, where others will perform an IUI when 3 of 4 dominant follicles are present. This will inevitably influence the chance on a multiple pregnancy. Another example is the SET versus DET trials, which were carried out in good prognosis patients and may therefore not be applicable in the general subfertile population.

Interpretation

The 15 studies on IVF that were powered to show a 50% reduction in multiple pregnancies evaluated a number of interventions to improve pregnancy rates, such as alternative culture media or stimulation protocols, but were not specifically designed to prevent multiple pregnancies. The average multiple pregnancy rate in these studies was extremely high (35%) compared to generally reported multiple pregnancy rates of 21% after ART in Europe (Ferraretti *et al.*, 2012). Twelve of the 15 studies were published before 2008, including collected data of years before the publication, when multiple pregnancies were less likely to have been considered a complication of ART treatment. It is easier to show a clinically meaningful reduction in multiples where the background rate is high.

There was a small increase in the percentage of trials reporting on multiple pregnancies after the ESHRE consensus report in 2003 (Land and Evers, 2003). An explanation might be that the majority of the trials were published before 2003 and trials published in the years just after the consensus report were carried out without the knowledge of this report. The conduct of a randomised controlled trial, including patient recruitment, data collection, followed by preparation, submission, peer review and publication of a manuscript can take several months. There is also an understandable delay in including new RCTs in Cochrane reviews, since updating the reviews also takes time.

An alternative approach towards evaluation of strategies aimed at preventing multiple pregnancies is to study the non-inferiority of an intervention, which is likely to reduce or even prevent multiple pregnancies, compared to control interventions. Examples of such strategies are tubal reconstructive surgery or IVF with elective Single Embryo Transfer (SET) as alternatives for ovarian hyperstimulation or IVF with two or more embryos (Gomel, 2007, Gerris *et al.*, 2002). We found ten non-inferiority studies, half of them comparing single to double embryo transfer (Gerris *et al.*, 1999; Martikainen *et al.*, 2001; Thurin *et al.*, 2004;

Lukassen *et al.*, 2005; Montfoort *et al.*, 2006). Two other studies were not designed to avoid all (dizygotic) multiple pregnancies, but to reduce the number of multiple pregnancies or the number of high-order multiple pregnancies in IVF (Heijnen *et al.*, 2006 and Vauthier-Brouzes *et al.*, 1994). A further study compared the difference in the embryo-transfer on day 3 or on day 5 on the outcome multiple pregnancy (Frattarelli *et al.*, 2003), whereas yet another study was conducted to assess the number of oocytes retrieved in IVF after pre-treatment with an oral contraception or after standard IVF protocol, but not to show a difference in the number of multiple pregnancies (Huirne *et al.,* 2006). The last of these 10 studies assessed prevention of multiple pregnancies by a low-dose step-up protocol in intra-uterine insemination (Sengoku *et al.*, 1999). Three of the five studies demonstrating the effectiveness of SET in reducing the twin rate in the study population compared to double embryo transfer, had sufficient power to show a reduction in multiple pregnancies. However, it should be noted that the inclusion criteria were limited to couples that all had a good prognosis, as only younger women with good quality embryos could participate in these studies (McLernon *et al.*, 2010). Consequently, the results and conclusions of these non-inferiority studies may therefore not be extrapolated to all women undergoing IVF, but only to those with a good prognosis, i.e. those with good quality embryos who are younger than 36 years.

Multiple pregnancies are generally considered an adverse outcome in ART. Although the contribution of ART to the absolute number of women with a multiple pregnancy is considerable, the consequences for the average individual woman undergoing IVF are less, as the majority of couples either conceive of a singleton pregnancy or do not become pregnant at all. In addition, not every multiple pregnancy ends in a poor outcome, as most multiple pregnancies carry on till term or near term, resulting in the birth of two healthy children (van Wely *et al.*, 2006). Outcomes in twin pregnancies resulting from IVF are comparable to those in spontaneously conceived twins (Vasario *et al.,* 2010).

CONCLUSION

In conclusion, multiple pregnancy rates are poorly reported in studies on interventions in reproductive medicine and most studies are underpowered to show a difference in multiple pregnancies. Studies designed to show a difference in multiple pregnancies were unable to show convincing differences between alternative strategies due to small numbers of multiple pregnancies in intervention as well as treatment groups. Use of standard meta-analysis techniques are unable to aggregate data on a number of interventions across different populations to reduce multiple pregnancies. Network meta-analysis is able to combine all the available evidence and might be an option. At present, clinical decisions concerning fertility interventions about reduction of multiple pregnancies, are intuitive rather than evidence-based.

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