Randomized controlled trials in reproductive medicine

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Chapter 4

How are neonatal and maternal outcomes reported in randomised controlled trials (RCTs) in reproductive medicine?

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ABSTRACT

Study question: How do randomised controlled trials (RCTs) in reproductive medicine report maternal and neonatal outcomes, specifically singleton live birth?

Summary answer: Despite the widespread appeal to use singleton live birth as the outcome measure in subfertility trials, 80% of RCTs fail to do so, and fail to report neonatal and maternal outcomes.

What is known already: The aim of reproductive medicine is to assist subfertile couples in their wish to have children. A decade ago it was proposed to use singleton live birth as the outcome measure. We assessed whether clinical research has followed this recommendation, and how neonatal/maternal outcomes are reported.

Study design, size, duration: A review of the published literature from 1 January 1966 to 31 December 2012 was performed using the Cochrane database. We compared the time periods before and after 2004; the year after ESHRE recommended the use of singleton live birth.

Participants/materials, setting, methods: We searched the Cochrane database for RCTs in reproductive medicine, and recorded the number of studies that used singleton live birth as the outcome measure. We also recorded the reporting of neonatal and maternal outcomes.

Main results and the role of chance: We identified 910 RCTs that reported on fertility treatments, of which 182 RCTs (20%) reported on singleton live birth (before 2004 96/518 (19%); after 2003 86/392 RCTs (22%). Singleton live birth was the primary outcome in 68 RCTs (7.4%). Only 44 RCTs (4.8%) reported on neonatal outcome, while 52 RCTs (5.7%) reported on maternal outcome.

Limitations, reasons for caution: We only included Cochrane reviews, thus report here only on the higher quality studies. The actual reporting on maternal and neonatal outcome may even be lower when less quality studies were also included.

Wider implications of the findings: Although a decade ago singleton live birth was recommended as the outcome measure of reproductive medicine research, this has not been followed; currently, most clinical research in reproductive medicine does not report beyond the occurrence of pregnancy.
INTRODUCTION

The aim of reproductive medicine is to assist couples with an unfulfilled child wish to have a healthy child, or, if wanted, healthy children. A major breakthrough in the field of reproductive medicine has been the introduction of IVF.

In the early years of IVF success rates were low; therefore the transfer of multiple embryos was introduced. After the initial years of increasing success rates, concerns were raised about the safety of multiple embryo transfer, particularly in view of the high rate of multiple pregnancies (Schieve et al., 1999). Multiple pregnancies are known to have a higher risk of complications for both mother and offspring. Women are more at risk for developing pre-eclampsia and labour complications requiring Caesarean section (Campbell and Templeton, 2004). Children born from multiple pregnancies have an increased chance of for being growth restricted or being born preterm (ESHRE Capri Workshop Group et al., 2000).

In view of these concerns, the outcome measures that should be used to assess the effectiveness of assisted reproduction techniques (ART) are a frequently discussed subject.

In 2003, during a European Society for Human Reproduction and Embryology (ESHRE) consensus meeting, it was agreed that although ART is applied on a large scale in Europe, risks and complications are poorly documented. Therefore the outcome measure of ART and non-ART should be singleton live birth, and multiple pregnancies should thereby be regarded as a complication. It was also recommended that registries should include data on neonatal and maternal morbidity and mortality (Land and Evers, 2003).

This recommendation fuelled a fundamental debate series on the most relevant standard of success in assisted reproduction. Proposed outcomes varied from singleton live birth per cycle initiated (Wennerholm and Bergh, 2004) and Birth Emphasizing a Successful Singleton at Term (BESST) (Min et al., 2004) till the percentage of elective single embryo transfer (eSET) (Land and Evers, 2004) and delivery rates per oocyte retrieved (Germond et al., 2004). This debate never led to new recommendations and as such it would seem that singleton live birth is currently the accepted outcome.
measurement. What we do not know however is whether this outcome measure is indeed reported in current literature.

The aim of this review was therefore to determine whether the recommended outcome measure ‘singleton live birth’ is used as outcome measure in subfertility trials. In addition, we assessed whether studies report on neonatal and maternal morbidity and mortality.

MATERIALS AND METHODS

Search Strategy
The database of the Cochrane Menstrual Disorders and Subfertility Group was searched for systematic reviews on interventions in reproductive medicine. In June 2013 all identified reviews were screened by two reviewers (MMvR and MB) and selected by title. The selected systematic reviews were categorized as reporting on IVF, ICSI, intrauterine insemination (IUI), ovulation induction (OI), or other reproductive treatments, for example tubal surgery or acupuncture.

Inclusion and exclusion criteria
We included all RCTs reported in these reviews. If an RCT was included in more than one review, data were only listed once.

Analysis
All included RCTs were searched for reporting of singleton live birth as outcome measure, or a descriptive form of singleton live birth, i.e. ‘healthy singletons’ or ‘take home baby rate’ when differentiated between singleton and multiple pregnancies. If one of these outcomes was mentioned, the RCT was evaluated in detail with respect to neonatal (after achieving ongoing pregnancy) and maternal outcome. We did not list data on miscarriages and early pregnancy loss. Stratification of the studies on year of publication was performed to register whether a change took place in reporting on singleton live birth after the ESHRE consensus report in 2003. We chose to compare the reporting on neonatal/maternal outcome in the periods before and after 2004, since this was the year after the ESHRE recommendation was published.
How are neonatal and maternal outcomes reported in randomised controlled trials (RCTs) in reproductive medicine?

To compare data from the various studies we used definitions that were provided in the ICMART (International Committee for Monitoring Assisted Reproductive Technology) glossary (Zegers Hochschild et al., 2009). In this glossary, singleton live birth is defined as a pregnancy that resulted in the birth of at least one baby born alive, independent of gestational age. Preterm birth is defined as a live birth or stillbirth that occurred after at least 20, but before 37, completed weeks of gestation. Congenital anomalies are defined as all structural, functional, and genetic anomalies diagnosed in aborted fetuses, at birth, or in the neonatal period. Neonatal complications in general are not defined in the ICMART glossary and we therefore listed all neonatal outcomes that were available from the publications; gestational age, congenital anomalies, low birthweight, intra uterine growth restriction, perinatal death.

RESULTS

Search strategy

Our search of the Cochrane database identified 87 reviews comparing clinical trials in the field of reproductive medicine, summarizing 910 RCTs. In total, 182 out of 910 RCTs (20%) reported on singleton live birth. These RCTs were searched for further information on neonatal and maternal outcome. An overview of the ratio between RCTs reporting on- and not reporting on singleton live birth, neonatal and maternal outcome is provided in Figure 1.

Figure 1: Number of RCTs reporting on singleton live birth, neonatal and maternal outcome in the period from January 1966 – January 2011.

* Abbreviations: OI: Ovulation induction, IUI: intra uterine insemination
**RCTs published before and after 2004**

Out of the 910 RCTs evaluated for this review, 518 were published before January 2004, of which 96 RCTs (19%) reported on singleton live birth, and 30 RCTs used singleton live birth as primary outcome measure (6%). Of the total 910 RCTs, 392 were published after December 2003, of which 86 (22%) reported on singleton live birth. As primary outcome, singleton live birth was reported in 38 studies (10%).

**Results on IVF/ICSI trials**

There were 555 RCTs that reported on IVF or ICSI of which 126 (23%) reported on singleton live birth. A detailed overview is provided in table 1. Singleton live birth was the primary outcome in 49 studies (9%). Neonatal outcome was only mentioned in 25 RCTs (4.5%). Maternal outcome was mentioned in 34 RCTs (6.1%), most trials only reported on ovarian hyperstimulation syndrome.

**Results on IUI trials**

There were 159 RCTs that reported on IUI, of which 28 (18%) reported on singleton live birth. A detailed overview is provided in table 2. Singleton live birth was the primary outcome in 9 studies (6%). Neonatal outcome was reported in 9 RCTs (5.7%), while 10 RCTs (6.3%) reported maternal outcome.

**Results on OI trials**

Out of the 57 trials that reported on OI, 12 reported on singleton live birth (21%). A detailed overview is provided in table 3. Singleton live birth was the primary outcome in 5 studies (9%). Only 3 studies (5.3%) reported on neonatal outcome and 6 studies (10.5%) reported on maternal outcome.

**Results on other reproductive treatment trials**

Out of the 139 RCTs that reported on other interventions, 16 reported on singleton live birth (12%). A detailed overview is provided in table 4. Singleton live birth was the primary outcome in 5 studies (4%). Only 7 studies (5.0%) reported neonatal outcome. Two studies (1.4%) reported on maternal outcome.
How are neonatal and maternal outcomes reported in randomised controlled trials (RCTs) in reproductive medicine?

Table 1: Overview of neonatal and maternal outcome reported in RCTs on IVF/ICSI

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<thead>
<tr>
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<tbody>
<tr>
<td>Total:</td>
<td></td>
<td>292</td>
<td>263</td>
</tr>
<tr>
<td>Reporting on singleton live birth</td>
<td></td>
<td>63 (22%)</td>
<td>63 (24%)</td>
</tr>
<tr>
<td>Singleton live birth as primary outcome</td>
<td></td>
<td>25 (9%)</td>
<td>24 (9%)</td>
</tr>
</tbody>
</table>

**Neonatal outcome:**

- Gestational age: 4
  - van Dijk et al., 1979, Martikainen et al., 2001, Kilani et al., 2003, Weissman et al., 2003
  - Hughes et al., 2004, Lukassen et al., 2005, Andersen et al., 2006, Babayof et al., 2006, Heijnen et al., 2006, Heijnen et al., 2007, Reindollar et al., 2009, Elgindy et al., 2011

- Congenital anomalies: 3
  - Balakier et al., 2009, Meyer et al., 2009

- Low birth weight: 1
  - Martikainen et al., 2001
  - Hughes et al., 2004, Lukassen et al., 2005, Andersen et al., 2006, Heijnen et al., 2006, Heijnen et al., 2007, Meintjes et al., 2009, Reindollar et al., 2009, Haapsamo et al., 2010

- Intra-uterine growth restriction: 0
  - Haapsamo et al., 2010

- Stillbirth: 1
  - Goverde et al., 2000
  - Galindo et al., 2009, Mastenbroek et al., 2007

- Neonatal death: 0
  - Elgindy et al., 2011

- Healthy: 2
  - Simon et al., 2003, Weissman et al., 2003
  - Blockeel et al., 2008, Balakier et al., 2009

- Other: 0
  - Doody et al., 2009

**Maternal outcome:**

- OHSS: 16
  - Ludwig et al., 2001
  - Haapsamo et al., 2010

- Hypertensive disorders: 1
  - Ludwig et al., 2001

- Infection: 0
  - Haapsamo et al., 2010

- Psychological well being: 1
  - Ludwig et al., 2001
  - Heijnen et al., 2007

*serious adverse events without further specifications
Table 2: Overview of neonatal and maternal outcome reported in RCTs on intra-uterine insemination

<table>
<thead>
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<tbody>
<tr>
<td>Total</td>
<td>99</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Reporting on singleton live birth</td>
<td>15 (15%)</td>
<td>13 (22%)</td>
<td></td>
</tr>
<tr>
<td>Singleton live birth as primary</td>
<td>2 (2%)</td>
<td>7 (12%)</td>
<td></td>
</tr>
<tr>
<td>outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neonatal outcome:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Shalev et al., 1995, Guzick et al., 1999, Vandermolen et al., 2001 Sahin et al., 2004, Moll et al., 2006, Legro et al., 2007, Bhattacharya et al., 2008, Johnson et al., 2010</strong></td>
<td><strong>Legro et al., 2007 Legro et al., 2007 Legro et al., 2007 Moll et al., 2006</strong></td>
<td><strong>Legro et al., 2007 Legro et al., 2007 Legro et al., 2007 Moll et al., 2006</strong></td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>Legro et al., 2007</strong></td>
<td></td>
<td><strong>Legro et al., 2007</strong></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Intra uterine growth restriction</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>Moll et al., 2006</strong></td>
<td></td>
<td><strong>Moll et al., 2006</strong></td>
</tr>
<tr>
<td>Neonatal death</td>
<td>0</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>Healthy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td></td>
<td><strong>Palomba et al., 2005</strong></td>
<td></td>
<td><strong>Palomba et al., 2005</strong></td>
</tr>
<tr>
<td><strong>Maternal outcome:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OHSS</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>Johnson et al., 2010</strong></td>
<td></td>
<td><strong>Johnson et al., 2010</strong></td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>Agarwal et al., 2004</strong></td>
<td></td>
<td><strong>Agarwal et al., 2004</strong></td>
</tr>
<tr>
<td>Psychological well being</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td><strong>Legro et al., 2007, Bhattacharya et al., 2008</strong></td>
<td></td>
<td><strong>Legro et al., 2007, Bhattacharya et al., 2008</strong></td>
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* perinatal death
How are neonatal and maternal outcomes reported in randomised controlled trials (RCTs) in reproductive medicine?

Table 3: Overview of neonatal and maternal outcome reported in RCTs on ovulation induction

<table>
<thead>
<tr>
<th>RCTs on ovulation induction</th>
<th>Number RCTs (percentage)</th>
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<tbody>
<tr>
<td>Total</td>
<td>34</td>
</tr>
<tr>
<td>Reporting on singleton live birth</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>Singleton live birth as primary outcome</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**Neonatal outcome:**

- **Gestational age**
  - Mc Faul et al., 1990: 1
  - Bayram et al., 2004: 1
- **Congenital anomalies**
  - Mc Faul et al., 1990: 0
  - Abdellah et al., 2011: 1
- **Low birth weight**
  - Abdellah et al., 2011: 0
- **Intra uterine growth restriction**
  - Abdellah et al., 2011: 0
- **Stillbirth**
  - Abdellah et al., 2011: 0
- **Neonatal death**
  - Abdellah et al., 2011: 0
- **Healthy**
  - Abdellah et al., 2011: 0
- **Other**
  - Abdellah et al., 2011: 1*  

**Maternal outcome:**

- **OHSS**
  - Abdellah et al., 2011: 3
- **Hypertensive disorders**
  - Abdellah et al., 2011: 0
  - Abdellah et al., 2011: 1
- **Infection**
  - Abdellah et al., 2011: 0
  - Abdellah et al., 2011: 1
- **Psychological well being**
  - Abdellah et al., 2011: 0
  - Abdellah et al., 2011: 1

*bad perinatal outcome, not further specified
Table 4: Overview of neonatal and maternal outcome reported in RCTs on other reproductive treatment

<table>
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<tbody>
<tr>
<td>Total</td>
<td>93 (67%)</td>
<td>46 (33%)</td>
<td></td>
</tr>
<tr>
<td>Reporting on singleton live birth</td>
<td>12 (13%)</td>
<td>4 (9%)</td>
<td></td>
</tr>
<tr>
<td>Singleton live birth as primary outcome</td>
<td>3 (3%)</td>
<td>2 (4%)</td>
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Neonatal outcome:

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Gestational age</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intra uterine growth restriction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Omu et al., 1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Healthy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1*</td>
<td>0</td>
</tr>
<tr>
<td>Omu et al., 1998</td>
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Maternal outcome:

<table>
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<tbody>
<tr>
<td>OHSS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Saitet et al., 1974, Rock et al., 1984</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological well being</td>
<td>0</td>
<td>0</td>
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</table>

* fetal distress

DISCUSSION

We aimed to evaluate the use of singleton live birth as an outcome measure in reproductive medicine trials, both before and after this had been recommended by ESHRE in 2003. Our review shows that singleton live birth as an outcome measure in reproductive medicine trials is implemented in a minority of the RCTs. From 2004 22% of the published studies used singleton live birth as outcome measure, as compared to 19% of the studies before 2004. Although we found a rise in reporting singleton live birth in trials on IUI and OI, this had limited impact in view of the large number of trials on IVF/ICSI.
We also found minimal reporting on neonatal and maternal outcome. Although there is no general recommendation to report on the outcome, records of safety parameters in RCTs can be useful when differentiating between several treatment options. Thereby it is clear that final conclusions on safety should be based on cohort studies.

Limitations
We realize that using Cochrane reviews carries the risk of selection bias; not all trials are included in Cochrane reviews. However, we feel that if such a selection would be present, it would have led to selection of the higher quality studies. We therefore think that our approach contains the appropriate studies, representing the randomised studies of the highest quality in reproductive medicine, i.e. those most likely to change clinical practice. The reporting rate of neonatal and maternal outcomes might even be lower if lower quality studies were included.

Strengths
Our review evaluates a large number of trials, which resulted in an accurate overview of the outcomes used in trials on reproductive medicine. This review indicates that there is a large heterogeneity between outcome measures reported in clinical trials in reproductive medicine. Comparisons between trials are therefore difficult to make. Editors should initiate a consensus meeting to determine the outcome measures that should be used in clinical trials in reproductive medicine and formulate recommendations. These recommendations should be followed by authors to improve the overall quality of clinical research in reproductive medicine.

CONCLUSION
In conclusion, use of the outcome measure singleton live birth, which was recommended by ESRHE in 2003, is not being implemented in clinical research.
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Wennerholm UB, Bergh C. What is the most relevant standard of success in assisted reproduction? Singleton live births should also include preterm births. *Hum Reprod* 2004;9:1943-1945