Randomized controlled trials in reproductive medicine
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Chapter 5

Ongoing pregnancy qualifies best as the primary outcome measure of choice in trials in reproductive medicine: an opinion paper

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Chapter 5

**ABSTRACT**

The most appropriate primary outcome measure for reproductive medicine has been discussed frequently. In 2003 the European Society for Human Reproduction and Embryology (ESHRE) recommended that the outcome measure of assisted reproductive techniques (ART) and non-ART should be ‘singleton live birth’ (Land and Evers, 2003).

Although live birth is indeed the aim of clinical practice, and there is no discussion that it should be reported in infertility trials, we hereby provide arguments that plead for using ‘ongoing pregnancy’ as the primary outcome in such trials. We feel that ongoing pregnancy best serves the many purposes of a primary outcome and best reflects the effectiveness of a treatment.
Ongoing pregnancy qualifies best as the primary outcome measure of choice in trials in reproductive medicine: an opinion paper

INTRODUCTION

The choice of the most relevant primary outcome measure in comparative effectiveness research in reproductive medicine is subject to debate. In 2003 the European Society for Human Reproduction and Embryology (ESHRE) recommended that the outcome measure of assisted reproductive techniques (ART) and non-ART should be ‘singleton live birth’ (Land and Evers 2003). The outcome ‘singleton live birth’ is perfectly in line with clinical practice as one of the main aims of fertility treatment is to help subfertile couples to get a healthy child. Therefore, we believe that every trial in reproductive medicine should, beyond any doubt, report on singleton live birth.

We question the use of singleton live birth as primary outcome in infertility trials, because it overlooks the fact that a primary outcome in comparative effectiveness research serves many purposes.

In this paper we will discuss arguments why the outcome ‘ongoing pregnancy’ instead of singleton live birth better serves the purposes of a primary outcome and why it better reflects the effectiveness of comparative effectiveness research. We thereby choose to define ongoing pregnancy as a viable intrauterine pregnancy of at least 12 weeks duration confirmed on an ultrasound scan.

ARGUMENTS

There are several arguments why ongoing pregnancy, compared to live birth, better serves the many purposes of a primary outcome.

First, the incidence of ongoing pregnancy is higher than the incidence of live birth and thereby reduces the required sample size. Second, when ongoing pregnancy is used interim analyses can be performed six months earlier compared to when live birth is used.

The timesaving explained by these first two arguments cause the results of trials to become available sooner to clinicians and patients. Moreover, since the interim analyses can be performed six months earlier, futility can be tested in advance before the
recruiting of patients has ended. This reduces exposure of the study participants to the inferior treatment and saves time and trial resources.

Third, compared to live birth, ongoing pregnancy is less subject to random error not related to the treatment under study. Due to pregnancy loss between 12 weeks of gestation and the birth of the child, which occurs in approximately in 5% of ongoing pregnancies (Clarke et al., 2010), the use of ongoing pregnancy will result in estimates of the treatment effect that are more precise. More specifically, treatments can only differ in live birth rate without differing in ongoing pregnancy rate, if one or both treatments would affect pregnancy loss after ongoing pregnancy in a systematic way.

In addition, excluding the effect of pregnancy loss between 12 weeks of gestation and the birth of the child by using ongoing pregnancy rate leads to less uncertainty around the truth of conclusions, since there is a 5% higher event rate, thus positively affecting the precision of estimates of treatment effect.

Fourth, ongoing pregnancy rate represents the effectiveness of a treatment and is not obscured or masked by safety issues. For example, in vitro fertilization (IVF) with single embryo transfer (SET) followed by frozen embryo transfer (FET) results in equal ongoing pregnancy rates compared to IVF with double embryo transfer (DET), but in more live births due to the decreased safety risk of preterm birth, which is more prevalent in twin pregnancies (<1% versus 20%) (McLernon et al., 2010). In this comparison of treatments, ongoing pregnancy rate perfectly reflects treatment effectiveness while the identified difference in singleton live birth rate reflects both treatment effectiveness and safety.

Finally, using ongoing pregnancy as primary outcome instead of singleton live birth, does not ignore the wish of many patients who consider a twin pregnancy desirable, since this gives them a family with more than one child (Grobman et al., 2001, van Wely et al., 2006, Dancet et al., 2014).
DISCUSSION

Performing comparative effectiveness research is the only way forward to make well-considered treatment choices in daily medical practice. In the ideal world, treatment options should be weighed against each other and against watchful waiting in randomized controlled trials before a treatment is chosen as standard treatment. Nevertheless, the interpretation of results of comparative effectiveness research is sometimes difficult. This is, amongst others, due to the use of a variety of outcome measures rather than a uniform outcome measure. Therefore, we plead for a modified Consolidated Standards of Reporting Trials (CONSORT) statement for fertility trials to reduce the heterogeneity of reported outcome measures by trials and that both ongoing pregnancy and live birth are part of that. We do challenge whether live birth should be the primary outcome.

ESHRE’s recommendation in 2003 to use singleton live birth as the outcome of ART (Land and Evers 2003), did not affect the use of this particular outcome measure. An analysis of our group showed that the proportion of trials reporting on singleton live birth was 19% before and 22% after the ESHRE recommendation (Braakhekke et al., 2014). These low proportions were not only barely affected, but were also very low as confirmed by a recent literature review of clinical and randomized controlled trials (Dapuzzo et al., 2011). Moreover, the proportion of trials that used singleton live birth as primary outcome was even lower, 7% versus 9% (Braakhekke et al., 2014). We did not investigate the reasons for the lack of adopting this outcome. We hypothesize that a major reason might be the time and trial resource consuming follow up until the event of live birth. Also the wish of clinicians to publish the trial results quickly, make the results readily available to patients, or even personal motives, might play role.

Apart from the poor adoption of the proposed outcome measure, we also observed a variation in the definitions of all outcome measures, including ongoing pregnancy. Although a viable intra uterine pregnancy of 12 weeks gestation or more is the most frequently used definition for the outcome ongoing pregnancy, a consensus on this definition is lacking. We therefore plead not only for reaching consensus on the appropriate primary outcome measure in trials, but also on the definition of this outcome.
Finally, we suggest an extension of the CONSORT statement for infertility trials. Such a tailored CONSORT statement could be a major step towards better reporting. We want to stress that this new statement should be followed and that editors should require all authors of infertility trials to adhere to the statement. Thereby, hopefully, uniformity in the reported (primary) outcomes will be achieved which will, in turn, allow proper interpretation of comparative effectiveness research, thus improving treatment decisions for couples with an unfulfilled wish for a child.

**CONCLUSION**

Several arguments are in favor of using the primary outcome ongoing pregnancy instead of singleton live birth to estimate the true difference in effectiveness between treatments. This does not mean that singleton live birth should not be reported.
REFERENCE LIST


