Singleton birth at term: an old alarm or a new debate?†

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ABSTRACT: In 2004, Human Reproduction published a debate series focusing on the rising tide of multiple pregnancy associated with IVF. The premise of the primary report in that debate was that by considering IVF outcomes differently—by focusing on healthy singleton birth at term rather than clinical pregnancy, the standard currency at that time—the necessary shift toward reduced numbers of embryos transferred might be accelerated. The choice of end-point in that debate—Birth Emphasizing a Successful Singleton at Term (BESST)—was not an effort to ‘dumb down’ the complex equation linking risks and benefits. That balance is a dynamic and various mix of issues that clinicians discuss with patients on a daily basis. And BESST was certainly not proposed as a new primary outcome for application to other treatment modalities in reproductive medicine, such as ovulation induction. It was simply a responsible and brave call for change in the accelerating and competitive world of IVF.

Key words: IVF outcomes / multiple pregnancy / treatment effectiveness / adverse outcomes / morbidity

Introduction

It is my privilege to respond to the article by Braakhekke et al. (2015) that highlights the need to separately evaluate and discuss with patients, the safety and effectiveness of their treatment. And I couldn’t agree more with that sentiment: safety and effectiveness of fertility treatment need and deserve separate attention and communication. However, what struck me about the article was its assumption that a debate published in Human Reproduction in 2004 on the reporting of singleton birth after IVF, suggested otherwise—I disagree with that notion and will propose an alternative viewpoint below.

The Articles and the Arguments

The premise of the article by Braakhekke et al. (2015) is founded on the following opening statement:

In our field a number of potential outcome measures have been proposed which combine effectiveness and safety. Examples are singleton live birth per initiated treatment and birth emphasizing a successful singleton at term (BESST) (Min et al., 2004; Wennerholm and Bergh, 2004).

Braakhekke et al. (2015) are really referring to one outcome highlighted in only two articles from the same the debate series published in Human Reproduction in 2004 (Min et al., 2004; Wennerholm and Bergh, 2004): singleton birth after IVF. In the primary piece, David Healy’s group focused on singleton birth at term while Wennerholm and Bergh argued that singletons born preterm should also be included in this rubric (Min et al., 2004; Wennerholm and Bergh, 2004). The primary concern of both groups at that time was the morbidity associated with multiple pregnancy. In 2004, they were already leaders in the movement toward appropriate elective single embryo transfer (SET), recognizing that the perinatal morbidity and mortality associated with a multiple pregnancy rate of 30% following IVF was unacceptable. Also at that time, IVF programs were publishing their ‘success rates’ in ways that failed to focus on, let alone account for, the problem of complicated multiple pregnancy. Rates of clinical pregnancy, and even biochemical pregnancy, were the currency of the day.

What Were Min and Wennerholm Saying?

In the primary 2004 piece, Min et al. (2004) dissected the outcomes of a single Monash IVF year: 2001. From ~2000 cycle starts, they reported a clinical pregnancy rate of 19.6%, a 17% delivery rate, but only an 11.1% chance of singleton term live birth. Focusing on that 11% figure as a relevant clinical outcome was a bold move, at a time when competition and self-promotion fueled the presentation of data in the best possible light. What were they suggesting otherwise—I disagree with that notion and will propose an alternative viewpoint below.

† Dedication: In writing this, I’m reminded of David Healy’s enormous contribution to our field. He was a superb clinician-scientist, mentor and friend who died far too young.
decision-making across the board in reproductive medicine. The authors are and were far too smart for that. Their message was that the value of IVF is better understood when it’s metered more deeply, so perhaps consider BESST as a standardized and important outcome that might be used across centers? The subsequent piece in that debate, added the notion that a preterm singleton birth should also be included, with its outcome clearly reported and understood (Wennenholm and Bergh, 2004).

Has Singleton at Term Been Adopted as a Gold Standard for IVF Reporting?

Over the ensuing decade, a paradigm shift has occurred toward reduced numbers of embryos transferred, but the IVF community has been less enthusiastic in embracing singleton birth or BESST as a gold standard outcome. In fact, the end-point has not been reported or used in any consistent way at all, although the Canadian database, CARTR (Canadian ART Register), has included it as one of many outcomes reported since 2008 (Gunby, 2011). It is also worth noting that according to PubMed, the paper by Min et al. (2004) has only been cited 19 times, while Wennenholm and Bergh (2004) have been cited twice. These numbers again suggest that the composite outcome of singleton birth, at or before term, has not been taken up or used as any sort of panacea for the complex balance between risks and benefits in our field, as suggested in the lead article for the current debate (Braakhekke et al., 2015). BESST hasn’t even been used as a point of focus in the ongoing efforts to limit multiple pregnancy after IVF.

Evaluating and Discussing Effectiveness and Safety with Patients

Braakhekke et al. (2015) highlight what we actually do in reproductive medicine: clinicians weigh effectiveness and safety separately, and help patients do the same as they balance those often-competing forces in making informed choices about their treatment. And that’s what almost all studies have to do as well. Randomized controlled trials (RCTs) in reproductive medicine can’t be powered to detect differences in rare but serious adverse outcomes such as congenital fetal anomalies. Large simple trials in fields such as cardiac disease have that facility and are deliberately powered with some of those outcomes in mind, but that’s just not possible in our field.

In exploring their notion further, that singleton birth at term confuses or masks the complex relationship between safety and effectiveness, Braakhekke et al. (2015) consider a recent effectiveness trial of letrozole, but read its findings a little differently than others might (Legro et al., 2014). They suggest that Legro et al. were saying that ‘there were more congenital anomalies in the letrozole group, 4/102 versus 1/66’ when in fact they actually reported that:

> Our data indicate that anomaly rates are similar with the two treatments we evaluated, and these rates are also similar to the rate in a population of healthy, fertile women who conceived without undergoing treatment for assisted reproduction (5.8%).

Adding that:

> Further study with larger numbers of infants is needed to clarify the safety and teratogenic risks with letrozole relative to those with other infertility therapies.

Of course, a larger cohort study would be needed to address this question of safety because RTCS, necessary for evaluation of treatment effectiveness, would be far too expensive to use when assessing such rare but serious adverse outcomes. Legro et al. (2014) were simply supporting, rather than ‘making a case’ for, separating effectiveness from safety, as suggested by Braakhekke et al. (2015).

The study of elective SET by Thurin et al. (2004) may also have been taken out of context. This paper presents a nice mathematical example to use because of its large effect-size, with a 30-fold increase in twinning associated with double embryo transfer (DET). The primary outcome of that study though was as complex as they get: the overall costs of maternal and neonatal healthcare following SET versus DET. The study didn’t come close to focusing on the very simple ‘healthy singleton birth at term’ as a composite index of fertility treatment success, and why would it (Min et al., 2004)?

Conclusions

Eleven years ago, Min et al. (2004) were not proposing a compound outcome to simplify and cover the disparate bases of safety and effectiveness in reproductive medicine. They were actually sounding an alarm against the rising tide of multiple birth after IVF prevalent at that time, as well as the tendency for clinics to report their data in the most favorable and attractive light possible. They were reminding us that treatment outcomes involve and affect mothers and babies and that we should look more deeply than we were doing at that time, into the reality of IVF ‘success’. Also, with only 21 citations between the 2 papers, this end-point has evidently not been taken up over the past decade as a gold standard, not by the IVF community nor in other areas of reproductive medicine. In this field, effectiveness and safety are far too complex and interdependent since, to précis Braakhekke et al. (2015), the desired outcome of fertility treatment is also one of the patients. Different research tools are used for pragmatic reasons, to evaluate effectiveness and safety: relatively small RCTs and large cohort studies, respectively. In discussing data from these studies with patients, effectiveness and safety are indeed routinely considered and communicated separately, just as David Healy would have done back in 2004.

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Author’s role

E.G.H. wrote and revised the article.

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