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The next step to improving outcomes of IVF: Consider the whole treatment

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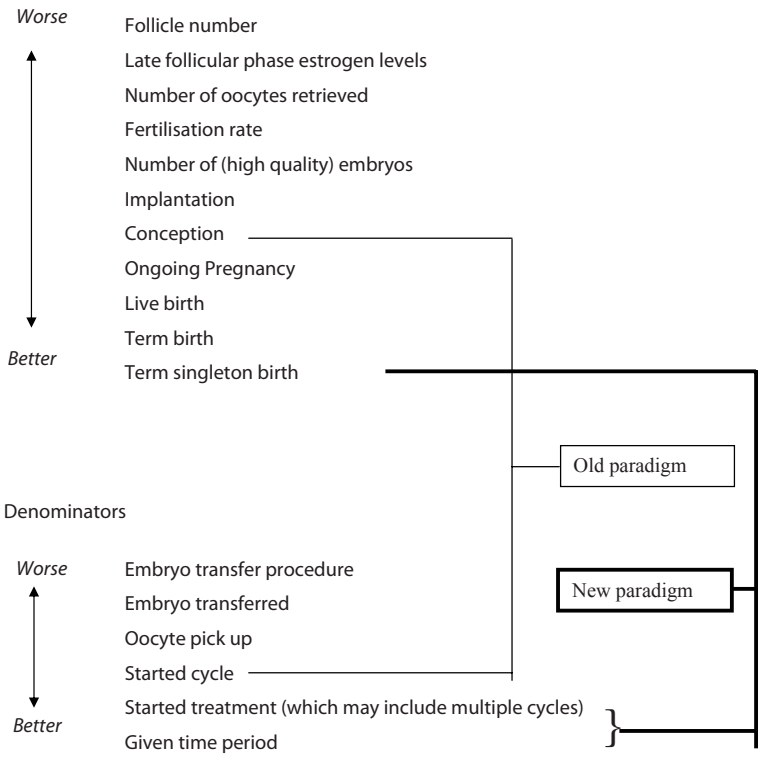
Introduction

A debate article in human reproduction proposed that 'the singleton, term gestation, live birth rate per cycle initiated should be considered the best endpoint for IVF' (84). It was suggested that this outcome definition reflects precisely what a subfertile couple wishes to know when they embark an IVF treatment. In our view, IVF outcomes should be defined in broader terms which reflect the interests both of the couple and those providing health care. A couple embarking on IVF are presently focused on the traditional numerators and denominators of outcome as shown in Table 1. The goal of their treatment is the chance of having a healthy baby after completing an *IVF treatment* consisting of a series of IVF cycles and subsequent replacement of frozen embryos. This should be weighed against the associated discomfort, complications and costs which they will encounter along the way. The outcome of a single cycle is of interest, but only as part of the whole treatment. The information patients, providers and policy makers require is the chance of delivering a healthy baby per treatment started (106,105) or per defined treatment period.

Table 1. Assessment of IVF treatment outcome: towards the optimal numerator and denominator.



Should these criteria become the means by which IVF outcomes are measured, a number of beneficial consequences would ensue.

Focusing on the whole treatment: consequences for clinical practice

Patient friendly stimulation protocols

Around 50% of those who initiate IVF will not conceive (107). This is partly due to the high drop out rates after an unsuccessful IVF cycle. European data reveal that up to 25% of patients who undergo a first IVF cycle refrain from further treatment (108), and are therefore deprived of additional chances of conceiving. This is not only due to costs, or poor prognosis (109) but also due to the stress and side effects of the treatment itself (32). By expressing results in terms of the delivery of a healthy baby per treatment started (or in a given time period), clinicians and scientists will be encouraged to develop and apply patient friendly stimulation protocols with less stress, discomfort, side effects and chances for complications such as the ovarian hyperstimulation syndrome.

The introduction of GnRH antagonists into clinical practice has enabled shorter treatment protocols to be applied since, in contrast to GnRH agonists, treatment can be limited to the days in the mid-to-late follicular phase truly at risk of a premature LH rise (58). Moreover, since this approach enables the endogenous inter-cycle FSH rise to be utilized rather than suppressed, it has opened the way to the development of mild stimulation protocols in which exogenous FSH administration is limited to the mid-late follicular phase (110,111,112,113).

Mild stimulation protocols may reduce drop outs from IVF and therefore increase the overall number of cycles per patient resulting in increased overall birth rates per started treatment. Shorter, patient friendly stimulation protocols may increase efficiency, enabling more cycles to be carried out in a given period than is possible with conventional stimulation protocols. Increasing exposure to chances of pregnancy while reducing exposure to the complications of conventional ovarian stimulation also offers a formula for reducing costs.

Single Embryo Transfer

In a debate series in Human Reproduction, Land and Evers suggest adopting an outcome measure - the corrected singleton live birth rate per cycle started - that rewards efficacy (many healthy singleton babies) and penalizes unsafety (multiple pregnancies) (88). We would agree that the ideal numerator for determining IVF outcome is a term singleton baby. However, Dickey et al proposed that multiple outcome measures are necessary when evaluating IVF success and that twin as well as singleton births should be counted as IVF successes (95). While healthy term twins may be perceived as a good outcome, twins

in general are at higher risk of neonatal morbidity and mortality (14,114), and the current consensus is that multiple pregnancies should be prevented. One approach to the problem of reporting IVF results may be the implementation of a scoring system where singletons 'count higher' than twins (score 1 versus 0.5) but both are recognised as preferable to no pregnancy and higher order multiple pregnancies (score 0). In this way twin pregnancies contribute to the pregnancy rate per treatment but are also relatively penalized (72).

Healthy Baby

In this, and other articles in the current debate series, the phrase 'healthy baby' is frequently referred to. Intuitively such an outcome is desirable not only for prospective parents but also for health care providers. The meaning of 'healthy' in this context remains to be defined. A recent study has added to concern that even singleton babies born after conventional IVF may be at increased risk of prematurity and the associated health risks (115). By inserting the word 'term' into the numerator of singleton baby, additional encouragement would arise to develop IVF treatments in which the risk of prematurity was further limited.

The integrated picture

Combining mild stimulation protocols with single embryo transfer is consistent with the emphasis on reducing complications for mother and child. This maybe at the price of a minor drop in pregnancy rate per cycle (46,37), but the same overall pregnancy rate per total IVF treatment may be achieved in the same amount of time, for similar costs with less patient stress and discomfort and most importantly with the virtual elimination of multiple pregnancies. It has recently been shown that counselling over the risks of multiple pregnancy may be insufficient to convince couples to opt for elective single embryo transfer (116). In contrast, if they can be reassured that their chance of achieving the goal of treatment will not be compromised, patients are receptive to the idea of transferring one rather than more embryos. Were IVF success rates to be expressed in terms of delivery of a term single baby per IVF treatment or in a certain time period, then such reassurance may be readily given, and single embryo transfer on a large scale more rapidly introduced.

We postulate that the combination of mild stimulation and single embryo transfer would reduce the overall costs of treatment, both to couples and society, partly by reducing the indirect costs related to pregnancy complications. This could be achieved despite an increased number of cycles compared to conventional IVF hyperstimulation and dual embryo transfer (117,35,37). We consider that the optimal numerator and denominator for defining outcome from IVF are the term, singleton birth rate per started IVF treatment (or per given period). Widespread adoption of this definition would be an important step towards achieving these goals.