

## COUNTERCURRENT

# Maximizing live birth rates cannot be the only key performance indicator of IVF

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## ABSTRACT

The success of IVF is currently measured by pregnancy or live birth rate only, without any consideration given to health outcomes for the woman and baby and the total cost of treatment. A successful IVF cycle should be redefined as the birth of a healthy singleton baby at term, without compromising the health and safety of the woman and baby achieved at the lowest possible cost. We recommend that the performance indices for an IVF programme should be based on a weighted scoring system according to live birth per embryo transferred, cumulative live birth rate over 1 year, total cost of treatment cycle and maternal and perinatal outcomes. This holistic approach would prevent the use of unnecessary high stimulation, unproven add-ons without regard for the welfare of the patients and would increase accessibility to IVF treatment.

The goalpost for IVF success is ever-changing. The target, which started as achieving a clinical pregnancy, changed to achieving a live birth, then cumulative live birth and, recently, to a goal of 'completing a family' from single oocyte retrieval cycle (Vaughan *et al.*, 2017). Understandably, the outcome of IVF for the woman and service provider alike is a live birth. The desperation to achieve this goal means that many women are willing to take any health risk and pay a high cost for treatment. It may also lead the service provider to recommend high stimulation and 'add-ons' with unproven benefits and potential health risks. Independent regulatory bodies and clinic websites publish pregnancy and livebirth rates (LBR), and not the incidence of ovarian hyperstimulation syndrome (OHSS) and complications for the woman and the birth weight and gestational age of babies born when presenting

outcomes of IVF cycles. Therefore, the basic principle 'first do no harm' does not seem to be a priority when measuring the success of IVF treatment.

## CAN ESCALATING TARGETS OF LIVE BIRTH RATE BE MET WITHOUT TAKING RISKS?

### Live birth rate per fresh embryo transfer cycle

A recent systematic review of all published data has confirmed that LBR in the fresh transfer cycle cannot be improved further once an average of 12–15 oocytes is retrieved (Law *et al.*, 2021). The risk of OHSS and other risks are minimal within this level of oocyte yield. Young women with good prognosis do not need to have a large number of oocytes collected for a successful outcome (Zhang *et al.*, 2021). We now realise, however, that the treatment outcome of older women

with a poor prognosis cannot be improved by increasing ovarian stimulation. Trying to improve fresh-cycle LBR just by increasing the number of oocytes or embryos only adds complications and increases the total cost of the treatment cycle.

### Cumulative live birth

An infinite number of oocytes are being chased to bank as many frozen embryos as possible to maximize the cumulative LBR, which has been shown to increase with oocyte yield, over and above the cohort that optimizes fresh cycle success rate (Law *et al.*, 2021). All the complications related to IVF treatment, however, also increase with the increasing cumulative LBR: the incidence of OHSS escalates in parallel when 15–25 oocytes are retrieved (Law *et al.*, 2021); the incidence of thromboembolism also increases (Magnusson *et al.*, 2018) and, importantly, the procedure-

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Declaration: The authors report no financial or commercial conflicts of interest.

related complications of oocyte retrieval e.g. pain, bleeding, ovarian torsion, become significant when more than 15–20 oocytes are collected (*Bodri et al., 2008; Levi-Setti et al., 2018*).

Gonadotrophin releasing hormone agonist trigger seems to have encouraged many clinicians to maximize the ovarian response and to dismiss the risk of OHSS. It is not, however, entirely prevented by agonist trigger, and the other risks of high oocyte yield remain. In fact, agonist trigger does not reduce the risk of OHSS significantly if it is followed by a fresh transfer (*Youssef et al., 2014; Connell et al., 2019*). Incidents of severe OHSS have been reported even when gonadotrophin releasing hormone agonist trigger is followed by freeze-all embryos. In a review of the literature, cases in which a genetic predisposition to OHSS had been implicated were presented (*Santos-Ribeiro et al., 2015*). Unsurprisingly, hospital admissions resulting from OHSS continue to occur across the globe, which is concerning.

### Completing family by ‘one-and-done’ approach

A recent trend to generate ‘sufficient’ numbers of oocytes from one stimulated cycle to ‘complete a family’ has added a seemingly attractive yardstick of success but at the same time it has given rise to safety concerns. Besides the controversy of how many children constitutes ‘a complete family’ and how many women and couples would wish to have more than one child, it has not yet been established how many oocytes can fulfil this objective. A study aiming to investigate this matter found only one out of four women could generate enough oocytes to create two or more children (*Vaughan et al., 2017*). Limited data suggest that over 15–25 oocytes are needed to give birth to two children and around 40 oocytes to achieve three live births from one oocyte retrieval cycle (*Vaughan et al., 2017; Connell et al., 2019*); this extreme response puts women’s health at risk, including OHSS, even with the use of agonist trigger (*Connell et al., 2019*). The side-effects and discomfort experienced by women with high ovarian response should not be ignored.

### HOW SHOULD IVF SUCCESS BE DEFINED?

The goal of IVF has long been set as ‘birth of a healthy singleton baby at term’. Indeed, the move towards single

embryo transfer is a typical example of acknowledging the balance between the success and risks. On the other hand, chasing the target of a maximum LBR, IVF programmes are increasingly becoming complex, expensive and unsafe. Routine use of intra-cytoplasmic sperm injection (ICSI) for non-male factor infertility and routine freeze-all embryos (with or without pre-implantation genetic testing) are the two examples that have added cost to the treatment with no proven benefit. Therefore, IVF practice seems to be polarized, with high intervention and expensive treatment at one extreme, and limited or no access to IVF treatment at the other. Consequently, the World Health Organization (WHO) has now called for a safe, effective and affordable fertility service to be instituted worldwide (*WHO, 2020*). We need a scoring system to appraise IVF performance indices under five broad headings with a weighted scale for each of the following indicators: LBR per embryo transferred; cumulative LBR after 1 year; the total cost per treatment cycle; incidence of hospital admissions caused by OHSS and other complications for the woman; and incidence of low birth weight and prematurity in babies.

The current unidimensional approach using merely the live birth rate per cycle of treatment as a performance indicator without any measure of health outcomes for the woman and her baby and cost of treatment is to be deplored.

### HOW COULD THE NEW TARGETS BE ACHIEVED?

The current drive to enhance the LBR by increasing the number of oocytes and embryos from a single cycle of treatment has led to the focus being on stimulation protocols to maximize the quantity and not the quality of oocytes and embryos. More attention needs to be focused on improving the conditions for implantation and achieving a successful fresh embryo transfer.

The emerging concept is that euploidy rates and LBR relate to age of the women, and do not depend on the number of oocytes or stimulation dose (*Irani et al., 2020; Zhang et al., 2021*). A low oocyte yield usually represents poor prognosis, which cannot be improved by intensifying stimulation. On the other hand, good prognosis patients could

produce enough oocytes and high-quality embryos, not requiring intense stimulation. We have recently shown that a single fresh-cycle LBR of 40.3% and cumulative LBR of 53.1% can be achieved with no incidence of severe OHSS in normal and high-responder women when a mild stimulation ( $\leq 150$  IU/day) is combined with judicious use of agonist trigger and freeze-all embryos in the event of high response (*Datta et al., 2021a*). Mild stimulation not only saves money on drug costs but also on the cost of treating OHSS and related complications by reducing hospital admissions. Conventional IVF is more expensive, and it does not translate into higher success (*Datta et al., 2021b*).

In conclusion, with the WHO’s initiative for global access to IVF treatment, urgent emphasis on safety and affordability of IVF treatment is needed. IVF treatment should aim to optimize success in relation to safety, cost, and burden of treatment. We have presented a scoring system that should supplant the current unsatisfactory unidimensional approach to measuring success.

Every healthcare and insurance system seems to take data on both success and safety (‘both sides of the coin’) into account when it comes to measuring outcomes for any therapeutic intervention and commissioning (or funding) treatments in other areas of medicine. This approach, however, is not currently applied when it comes to IVF treatment in many countries. With limited public funding available for IVF treatment globally, the sector needs to adopt a more ‘holistic’ approach to assessing and publishing performance indices and maintain a global registry (*Fauser, 2019*). The regulators and service funders (public bodies, insurance or self-funded patients) should demand complete and transparent information about IVF treatment outcomes. We have a responsibility to change the matrix of how we measure success of IVF treatment and implement in our practice and also in scientific publications and national and international registries.

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Received 13 October 2021; received in revised form 9 November 2021; accepted 12 November 2021.