Opinion

How should we define success in assisted reproduction? Is live birth rate the gold standard measurement?

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The dictionary defines “success” as the favorable or prosperous result of attempts or endeavors. This definition is too simplistic at times, especially as it relates to assisted reproduction technologies (ART). Currently, there is a consensus that live birth rates are the best measurement to assess the success of ART. This is evidenced by the multitude of scientific papers reporting on the success of ART using live birth rate as the outcome measure.

Success is viewed differently by clinicians and their patients or members of one medical discipline vs. their peers in a different field. For example, successful resuscitation of an extremely premature infant by the physician

would be considered a great achievement but may be regarded as a misfortune by the family as time goes by and a severe handicapped baby survives.

At the forefront of ART is classical IVF. Initially, achieving conception was regarded a success by clinicians performing ART. As time progressed and ART techniques were further refined, success was defined as a visibly viable pregnancy, whereas nowadays only a live birth is considered the gold standard of success. Since the media hunger for high impact news, it is understandable that the earlier work performed by Edwards and Steptoe, which resulted in an ectopic pregnancy and miscarriage, was not as highly publicized as the birth of Luisa Brown, who was the first full-term IVF birth [1]. However, the question remains whether we who provide ART should use the same standards or whether we should focus on the relative contribution of each professional participant. Indeed, an individual healthy full-term infant is the ultimate goal for both us and our patients. However, several obstacles hinder us from reaching this goal. Briefly, we use medications to harvest gametes from a woman and a man, and we process these gametes in the laboratory using micromanipulations and biochemical exposure, followed by incubation. Eventually, the embryos are placed into the uterus of the woman. During those processes, one has to be successful in yielding mature oocytes, accomplishing a good fertilization, and properly incubating the zygotes to promote cleavage. Therefore, success could differ depending on your perspective. For example, an embryologist would consider the transfer of high quality embryos into the woman a success. Two weeks later, a positive pregnancy test may result in a joyful embrace between the couple and the ART physician. However, what if this patient

Capsule Clinical pregnancy as a viable gestational sac should be used as a success predictor following ART

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miscarries during the 31st week due to placental abruption? Is this a failure of the IVF team? Or should fetal surveillance and monitoring throughout the pregnancy, including routine obstetric procedures, be considered part of ART? If one compares current obstetric practice to that from three centuries ago, then this may be the case.

Visualization of an gestational sac, but without any heart activity by ultrasonography; is it the failure of the physician who transferred the embryos or is it a success determined as the implantation of the transferred embryos. We are not aware any data indicating relationship with increasing early pregnancy losses with embryo transfer technique, but we are aware of data demonstrating inferior pregnancy rates with inexperienced physicians [2].

In considering live birth rate as the sole determinant of success, one becomes aware of many potential confounding factors in reports that have evaluated the success of an ART program using a comparison to specific control groups, in which the participants did not necessarily receive similar obstetric care or were not similar in terms of socio-economic status and general health parameters. For example, in countries where ART is paid for by patients, it is very likely that women who conceived after undergoing ART are from a higher socio-economic class, which would make a comparison to women of the general public somewhat irrelevant. However, if one reports outcome following controlled ovarian hyperstimulation (COH) protocols as well as the obstetric outcome, one should also postulate the mechanisms by which gonadotropins or GnRH analogues impacted 2nd or 3rd gestational trimester events. We believe that the management of an infertile couple during ART will mostly have an impact on the first trimester. Luteal phase support is recommended for ART and extends for up to 8 or 10 weeks of gestation, which is not required for spontaneous pregnancies [3]. In this regard, the early weeks of ART gestations warrant hormonal fine tuning by the IVF physician. The remainder of the pregnancy should be transferred to the relevant perinatology team.

It is important that some couples undergo ART not just because of difficulties conceiving but also to prevent the transmission of inherited diseases. In this scenario, a genetically competent healthy embryo is required, and conception with an unhealthy fetus is considered a failure rather than a success. An additional consideration is whether a fetus with Down syndrome generated from ART is considered a failure or success.

Indeed, most relevant reports assessing the effectiveness of IVF treatment modalities did not match women to controls based on their demographics, which could potentially affect the obstetric outcome (e.g., smoking, alcohol intake, social and economical factors, race, uterine abnormality, subseptate, unicornuate, underlying antiphospholipid

syndrome, or inherited thrombophilias, etc.). In addition, a clear definition of live birth was also missing in the majority of these reports. To our knowledge, none of these studies defined its major outcome to be the birth of a healthy full-term neonate. Furthermore, it is probable that the antenatal care of the participants in the control groups was not performed by the center that participated in the study. Therefore, results from these studies should be interpreted with caution.

Another mostly hidden aspect of counting live birth or miscarriage rates is the “per event” calculation. Strictly speaking, the live birth rate is significantly higher for twins compared to single births and the total miscarriage risk is lower for twins compared to single births. Vanished embryos commonly occur with multiple pregnancies; therefore, in the case of a live birth, it would not be considered a miscarriage [4]. The majority of clinical trials and metaanalyses in studies assessing the effect of gonadotropins and GnRH analogues in IVF did not take this into consideration when calculating the live birth rate [4–8].

World Health Organization defines live birth as the complete expulsion or extraction from its mother of a product of fertilization, irrespective of the duration of the pregnancy which after shows any evidence of life [9]. In this context, is it reliable to judge or compare a treatment modality or a newly designed laboratory technique for its effectiveness in ART in which only live birth rate has been targeted as success instead of clinical pregnancy rate? What is the difference between a 13th weeks aborted fetus than a delivered 20 weeks infant practically?

In addition, the timing for the earliest detection for pregnancy was not specified in the majority of studies. One could miss a vanished gestational sac or could not recognize a live embryo in a case of missed abortus in a twin conception if a transvaginal ultrasound was performed at 8 weeks rather than at 5.5 weeks of gestation. For statistical comparisons, if a control group has a higher multiple pregnancy rate, this will decrease the number of miscarriage cases and increase the live birth rate. On the other hand, if the major outcome has been assigned as a live birth instead of a clinical pregnancy, this will greatly decrease the statistical power and will result in non-significant differences. It is likely that the effect of this under-reporting will eventually disappear as the transfer of a single embryo is becoming the worldwide gold standard.

To conclude, we believe that to adequately reflect the effectiveness of the various infertility treatment modalities, the criterion of a visibly viable pregnancy should be used as the standard endpoint for assessing the success of ART. On the other hand, definition of success could be individualized by the participating parties to the treatment.

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