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Believing that transferring more embryos will result in increased pregnancy rates: a flawed concept: a SWOT analysis

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Abstract

A belief exists that transferring multiple embryos can improve pregnancy rates. However, this concept is flawed. Multiple factors affect outcomes when transferring embryos, endometrial receptivity, and rates of aneuploidy among them. In this article, we will discuss how factors can affect outcomes at IVF that are independent of the number of embryos transferred. It is important to understand the role of accessory factors on pregnancy rates to be able to counsel patients as per the number of embryos that should be transferred. An understanding of this concept will also lead to a realistic understanding of how multiple embryo transfers may result in better cumulative pregnancy rates than a single transfer of multiple embryos. Finally, we will present a SWOT analysis diagram to help guide clinical decision-making.

Keywords: Pregnancy rates, IVF, Single embryo transfer, Endometrial receptivity, Aneuploidy

Main text

A concept exists in infertility medicine, which is that pregnancy rates increase as more embryos are transferred [1]. We often hear this concept discussed in meetings, and stated by reviewers, and is one cause of the persistently elevated rates of double embryo transfer in certain regions [2]. However, this concept is likely flawed. Recently, Gleisher et al. published an article that argues that IVF success rates peaked in 2010 and have been decreasing since then [3]. They attribute this decrease to the increased use of elective single embryo transfer among other factors [3]. Although the use of single embryo transfer can decrease outcomes per transfer [4], particularly if the embryo selected turns out to be aneuploid, overall placing back more embryos will in many cases, not improve outcomes [5, 6].

In some situations, the probability of an outcome occurring is based on the cumulative probability of each part, i.e., if the chance of an embryo implanting is ¼ or 25%, if you transfer 4 embryos the chance of at least one implantation could be argued to be 4 × ¼ or 100%, which it is not. This statistical representation depends on each act segregating independently, or the likelihood of one thing occurring is independent of the others. An example of independent segregation is a coin toss. If you toss a coin 50 times and every time it lands heads, the chance of tails in the subsequent toss remains 50%. However, biologic systems often do not segregate independently.

Pregnancy after embryo transfer is dependent on multiple factors including uterine receptivity. There are women whose endometrium is sub-receptive (low probability of implantation) [7] or possibly even unreceptive. If one genetically normal embryo is returned to such a uterus or many are transferred, the probability of pregnancy would remain very low. It is also known that there are couples that produce a low percentage or even zero percent genetically normal embryos. In this second case, the chance of pregnancy whether you return one or 4 embryos may remain extremely low, if not zero. These are factors that cannot be overcome by transferring a

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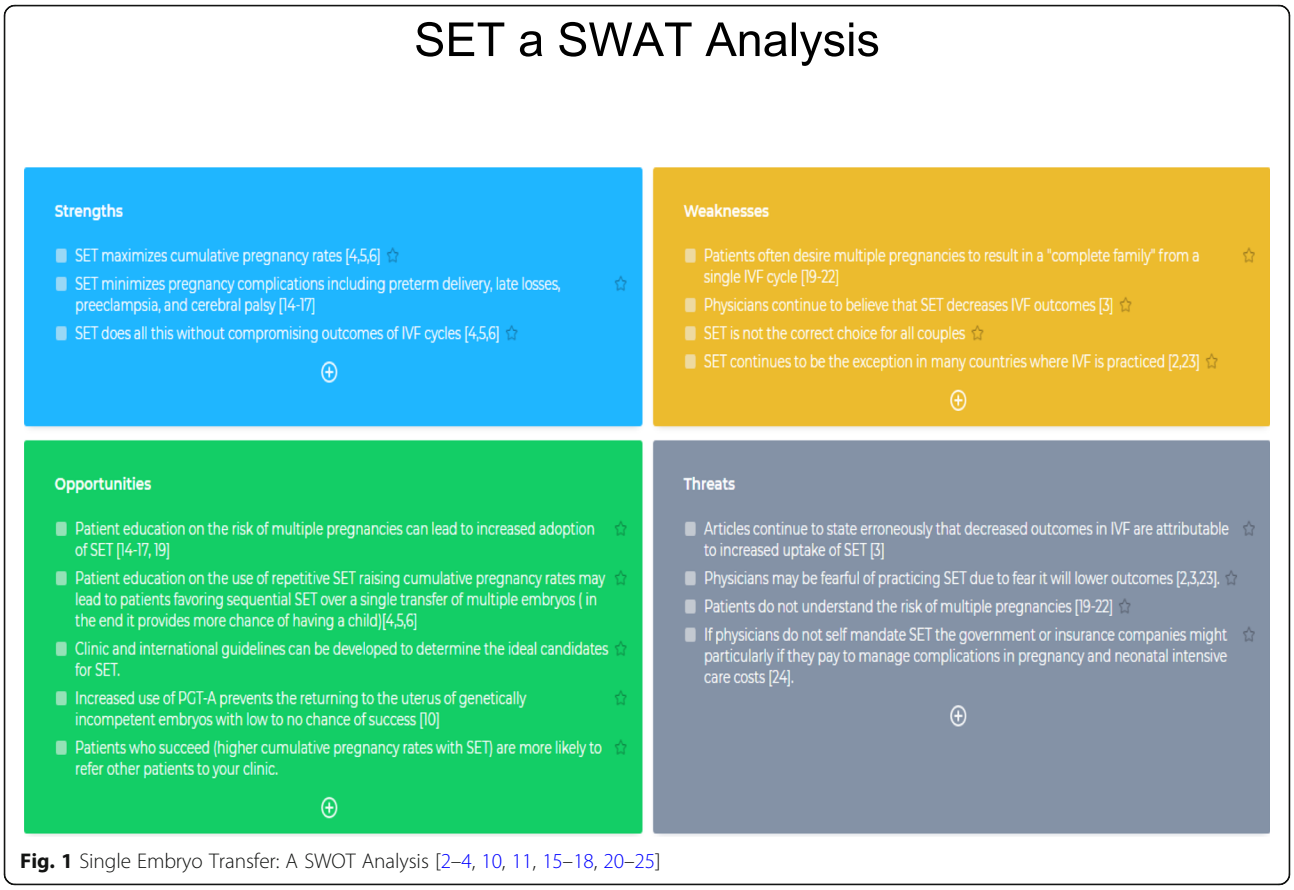

Fig. 1 Single Embryo Transfer: A SWOT Analysis [2–4, 10, 11, 15–18, 20–25]

greater quantity of embryos. Likely, the more genetically abnormal embryos that occur, the greater probability that a subsequently tested embryo is genetically abnormal and as such the probability of one embryo affects the others, i.e., not segregating independently.

Along the same lines, likely, transferring one or two blastocysts may not affect the pregnancy rates. This has been repetitively demonstrated in multiple studies, including one by us performed in older patients, those most at risk for genetic abnormalities of embryos [5]. We also demonstrated that sequential single blastocyst transfer in women 40 years of age or older twice, as compared to a one-time double blastocyst transfer, results in a higher cumulative pregnancy rates [6]. Suggesting that endometrial dys-synchrony may be overcome in a subsequent cycle and confirming that the endometrium plays an important role in the probability of pregnancy at any given embryo transfer [6, 8–11]. In a randomized study comparing transferring a single euploid blastocyst after trophectoderm biopsy or two untested embryos, transferring two embryos resulted in similar pregnancy and ongoing pregnancy rates but much high rates of multiple gestation (54% vs. 0%) [12].

Unscreened single vs. double blastocyst transfer resulted in equivalent live birth rates irrespective of age in another study [13]. On the other hand, other studies have shown increasing pregnancy rates transferring two as opposed to a single blastocyst [4, 14]. The difference between the findings of these studies likely represents the role of endometrial receptivity, transfer technique, and embryo genetics [8, 9]. A recent randomized study has brought the role of endometrial receptivity to the forefront of IVF outcomes. In a naïve patient population, screening with the endometrial receptivity assay and doing a personalized transfer resulted in significantly higher cumulative pregnancy rates (93.6%) compared with FET (P = 0.0005) and fresh embryo transfer groups (P = 0.0013) [15]. Importantly, the cumulative pregnancy rate per cycle was just south of 100% in the group screened with ERA as opposed to 80% in the other groups. This discrepancy highlights the role of endometrial receptivity on pregnancy outcomes at IVF [15].

Although transferring multiple embryos may impact the pregnancy rate per transfer, multiple pregnancies remain a risk [4, 6, 14]. We have known that this is the desired outcome for many of our patients, with the opportunity of at one time to complete their family when two children are delivered as twins. However, implications may not be well understood by patients even if consented. Our patients would not select to have a

child with cerebral palsy. Rates of prematurity and cerebral palsy are elevated in twins as compared to singleton pregnancies [16–18]. The problem with multiple pregnancies remains the higher risk of complications, both maternal and fetal/neonatal [17–19]. These complications include higher rates of miscarriage including late second trimester miscarriages, higher rates of preterm delivery, admission to the neonatal intensive care unit, cesarean section, fetal/neonatal death, preeclampsia, gestational diabetes [17–19]. There are many situations where a single embryo transfer makes more sense than multiple embryo transfer and would not be debated. This includes when transferring a genetically normal embryo and first-time IVF in a patient under 40 years of age particularly since in young maternal age aneuploidy rates are low. When multiple pregnancies occur, reduction to a singleton pregnancy is an option [20]. However, this is usually accompanied by an increased risk of miscarriage of both fetal sacs [20]. Therefore, conceiving a singleton pregnancy from the start will clearly have a lower risk than managing a multiple pregnancy.

SWOT stands for strengths, weaknesses, opportunities, and threats. It is a mechanism to capitalize on opportunities in the market place. When evaluating the role of single embryo transfer (SET) in IVF, the following SWOT diagram was developed. It becomes clear on analyzing this diagram that there are many reasons to practice SET and that there remain issues with the adoption of SET that can be overcome. Although SET is not ideal for all patients, many patients will benefit from its adoption (Fig. 1).

In conclusion, due to the inter-dependence of biologic system variables, caution should be used when believing transferring a greater number of embryos can increase the probability of pregnancy. Instead, effort should be placed into maximizing the probability of pregnancy for each embryo and as such minimizing the number of transferred embryos. There have been significant embryological advances during the last 10 years including the use of bench top and other high-quality incubators, low oxygen tension, and time-lapse imaging that have very positive implications on embryo quality and selection and that should make SET the rule rather than exception. Multiple embryo transfer had value historically, which is less valid today. These findings when combined with lower complications for the mother and child as part of a singleton birth favor the use of single embryo transfer in most cases.

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