In vitro fertilization twins: acceptable when desired, or iatrogenic complication preventable through elective single embryo transfer?

An obstetrician recently shared her emotionally draining experience managing live delivery of in vitro fertilization (IVF) twins at 20 weeks gestation (1). Over my 35 years in IVF I have heard of many pre-viable losses of IVF twins. Her wrenching account should be required reading for any IVF provider who allows transfer of two embryos outside of Society for Assisted Reproductive Technology (SART) guidelines.

Infertile couples easily lose perspective regarding the risks of multiple pregnancy. In this fertile battle, the two sides differ dramatically regarding patient autonomy. On the "pro" side of avoiding twins, at the first visit Gabe Garzo, Anja Pinborg and Brad Van Voorhis give couples the opportunity to seek another provider if they disagree with their clinics' policies. On the "con" side, championed by Eli Adashi, Norbert Gleicher, and Jean Parinaud, patient autonomy is given a strong role.

To explore the prevalence of these two sharply contrasting attitudes in the U.S., I spent many hours on SART.com collating the elective single embryo transfer (eSET) and twin rates of clinics with accessible data and reporting at least 20 transfers for women under age 35 for 2015. Unidentified raw data are given in an online supplement. If we arbitrarily estimate for these young women that following SART guidelines should result in at least 50% eSET, over two-thirds of IVF centers failed that test. One could argue the rate should be over 75%, but only 10 of 310 programs (3%) exceeded that threshold. We must presume that in a very large number of cases, the reason stated in the chart would indicate it was the couple's choice in spite of being informed of the risks.

Both sides acknowledge that risks are greater with a twin versus a singleton pregnancy. As Anja Pinborg points out, the appropriate comparison is the risks of an IVF twin pregnancy versus two sequential IVF singleton pregnancies, because the second, parous delivery has lesser risks. Because additional implantations that resorb are known to increase perinatal risk (2, 3), the information we need is the risks of a twin pregnancy with only two embryos transferred compared to two sequential singleton pregnancies, each with only a single embryo transferred.

Gabe Garzo has outlined the recently recognized consequences of early term (37–38 weeks) compared to full term (39–40 weeks) deliveries, which has a high prevalence in twins and is associated with an increased incidence of perinatal complications and mild learning deficits (cortical grey matter expands almost fifty percent and myelinated white matter triples in the last 4 weeks of gestation). The American Society of Obstetrics and Gynecology now recommends that repeat cesarean deliveries should not be scheduled before 39 weeks. We must also consider the difficulties in doing invasive prenatal testing with two fetuses and the consequences, including an increased risk of cerebral palsy, for the surviving offspring following resorption of an abnormal fetus. Cerebral palsy occurs more often with twins, particularly with very premature infants (4, 5). Importantly, cerebral palsy has been linked in singleton pregnancies to transfer of more than a single embryo. Singleton pregnancies with only a single embryo transferred appear to not have an increased risk. Very early delivery of twins can be accompanied by other severe, lifelong handicaps. Maternal mortality, fortunately rare, is also higher. I personally know of a mother of IVF twins who died of sepsis after delivery, and two others who died from severe post-partum hemorrhage. A few years ago, an American Society for Reproductive Medicine abstract described IVF maternal deaths due to severe preeclampsia. Even though rare, such enormous tragedies, which are less likely to occur with singleton pregnancies, must weigh heavily in this debate.

The two sides have sharply differing perspectives regarding the increased risks with twins. On the "pro" side, they are deemed unacceptable when the same success can be achieved with vitrification of the additional embryo followed by deferred transfer. The "con" side even terms those risks as mild, of questionable clinical significance, and justified by fulfilling couples' desires. Women are often allowed to proceed with fertility treatment with serious health issues, but it is difficult to justify the choice of a more hazardous twin pregnancy when only a more expeditious success, mildly reduced cost, or a desire for a second or third child is the couple's goal.

Healthcare costs are lower with two singleton pregnancies than one twin pregnancy. However, in the U.S., fertility care is usually out of pocket, whereas the higher costs of twins are mainly borne by insurance. The mean eSET rate among IVF programs in Massachusetts was 66% for women under age 35, presumably in part due to insurance coverage of both in that state. Such trends are very prominent in Scandinavia, as described by Anja Pinborg, where both are covered. There will be increasing rationing of new, sophisticated biotechnological advances in medical care due to limits of society's will or ability to provide them for everyone. Can we rationalize having people unable to benefit from a cure for cancer (as in the dramatic example of past U.S. president Jimmy Carter) or a fatal genetic disease (such as the 18 combined immune deficiency babies recently cured at UCLA) because patients are allowed to ignore national guidelines, adding major costs to the healthcare system? On the "con" side, an argument is posed that the cost calculation should account for lifetime earnings of the second offspring. However, if both embryos are sufficiently capable to implant together, the second embryo is likely to implant with a subsequent single embryo transfer. Major expenses must also include those from lifelong handicaps resulting from twin births.

SART has made highly commendable progress in achieving a continuing marked reduction of multiple pregnancies resulting from IVF, through education and guidelines regarding the number of embryos to transfer. Unfortunately, the decision by the Centers for Disease Control and Prevention (CDC) to report the rate of IVF twins as a percentage of started

TABLE 1

Mean single embryo transfer/implantation rate ratios, increasing in 0.25 increments from 0 to > 1.75, are shown for women under age 35 as reported to Society for Assisted Reproductive Technology for 2015.

	eSET/IR							
Variable	**0 < 0.25**	**0.25 < 0.5**	**0.5 < 0.75**	**0.75 < 1**	**1 < 1.25**	**1.25 < 1.5**	**1.5 < 1.75**	**≥1.75**
Twins/cycle start (mean)	15.13	15.34	12.54	10.75	7.52	5.39	5.41	5.45
Twins/live birth (mean)	33.17	32.96	26.25	21.92	15.5	12.44	12.67	15.71

Note: eSET = single embryo transfer; IR = implantation rate. Progressive decrease in percent twins per live birth with an increasing eSET/IR ratio.

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cycles underemphasizes this important complication by over 50% (directives in the original legislation dictated reporting outcomes using that denominator). The recent SART alignment with the CDC seems unfortunate and unnecessary, since SART would not have that constraint. To calculate the actual twin rate per live delivery, simply divide the twin rate per started cycle (line 3) by the percentage of live births × 100 (line 5) in the SART report. For example, the twin and live birth rates per started cycle for the first center in the report were 10.6 and 39.0, giving a twin rate per live delivery of 27.2, over 2.5 times what is reported. This effort should not be impaired by minimizing the incidence of a problem not yet solved. SART should prominently display the twin rate per live birth in a priority position on the first page of their report.

We can't ignore the elephant in the room. In the SART 2015 data for women under age 35 years, the eSET rate varied from 0 to 98, the implantation rate (IR) ranged from 11 to 83 (mean 43%) and the twin rate per live birth spanned 0 to 64%. Programs having an IR substantially below average would not have reasonable and competitive success rates without a strong patient autonomy policy. If all infertile couples were equal, the increased number of embryos would make up for the lower chance of each implanting and the twin rate would not greatly increase. However, some highly fertile couples can have a good IR regardless of suboptimal clinical and laboratory factors. If their individual IR was 75%, a simplified calculation of their twin rate would be 56% (0.75 × 0.75). This likely explains why programs with low IRs can have inordinately high twinning rates.

Simple logic indicates that the twin rate would increase as the eSET rate decreases and as IR increases. Therefore, twin risk would decrease as the eSET/IR ratio increases (the mean eSET/IR ratio in this data set was about 0.8). In Table 1 note the steady decrease of twinning with an increasing eSET/IR ratio. An interim goal could be that a program's eSET rate should exceed their IR rate (a ratio of 1). Ideally, each program should calculate its own twin rates, as outlined by Jean Parinaud.

Finally, Brad Van Voorhis has summarized the factors influencing the desire for twins and has described effective measures to educate patients. SART and the CDC have collaborated on developing educative materials and SART has developed an individualized success and risk profile for use by patients (https://www.sartcorsonline.com/Predictor/Patient). Unfortunately use of program-specific IR rates in those calculations is not feasible due to the low numbers for most IVF centers in each age category, yielding insufficient accuracy. In summary, efforts to further decrease twin rates with IVF should focus on patient education, commitment of individual program physicians, SART oversight of programs having consistently low eSET/IR ratios, increased insurance coverage of fertility treatment, and improved quality of underperforming programs so that higher implantation rates will result in greater use of eSET.

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