

Prevention of in vitro fertilization twins should focus on maximizing single embryo transfer versus twins are an acceptable complication of in vitro fertilization

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PRO: Prevention of in vitro fertilization twins should focus on maximizing single embryo transfer

Pro 1. Gabriel Garzo, M.D.

Twin pregnancy is an iatrogenic complication of in vitro fertilization (IVF) associated with severe as well as subtle adverse outcomes (1). With higher implantation rates (IRs) and refined cryopreservation protocols for extra embryos (2), many centers like ours worldwide have made single embryo transfer (SET) the default choice for most IVF couples. When accompanied by preimplantation genetic screening, elective SET (eSET) pregnancy rates at all ages have reached 50% or higher (3), whereas double embryo transfer (DET) would carry an unacceptable risk of twins. Equivalent or superior results can be achieved with sequential transfer of the two embryos (4–6). We provide detailed counselling at the initial visit so that a couple has the opportunity to seek another provider if they disagree with our center’s policy. Once a comprehensive presentation of the risks and alternatives has been made, it is our experience that most couples prefer single embryo transfer.



CON: Twins are an acceptable complication of in vitro fertilization

Con 1. Eli Y. Adashi, M.D., M.S.

The birth of twins need not invariably be viewed as an adverse outcome of ART (39). A uniform eSET policy may not meet patient expectations (40) and may be seen as arbitrary and not suited to their individual desires and circumstances (39, 40). Discretionary DETs have their place when preferred by the couple, absent overriding contraindications. Patient autonomy, long-standing infertility, and advancing age warrant nothing less. That said, a selective DET policy is not incompatible with the outlook that eSETs are preferable when feasible and agreed upon by both physician and patient.

The option of selective DETs has consistently been acknowledged for IVF programs and their patients by our national organizations. According to the most recent guidelines published in 2017 by the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology, the recommended limit for the number of blastocysts to

Received December 5, 2017; accepted December 5, 2017.

D.R.M. has nothing to disclose. E.Y.A. has nothing to disclose. G.G. has nothing to disclose. N.G. has nothing to disclose. J.P. has nothing to disclose. A.P. has nothing to disclose. B.V.V. has nothing to disclose.

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<https://doi.org/10.1016/j.fertnstert.2017.12.005>

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In addition to more serious risks outlined below, it is now known, compared to births at 39 weeks, early-term births (37–38 weeks) are associated with an increase in adverse neonatal outcomes by a magnitude of up to 4-fold at 37 weeks and 2-fold at 38 weeks (7, 8). These are primarily respiratory and with Caesarian delivery (9), which is the mode of delivery for most IVF twins, but also include other neonatal complications. Because the modal week (highest frequency) for assisted reproductive technology (ART) twin births is 37 weeks, 39.2% of twins are born early-term (1). If we add the risk of preterm birth (53.8% in this study) plus early-term, twins have over a 90% risk of being born before 39 weeks and at risk of an adverse outcome.

The brain grows rapidly during the final four weeks of pregnancy, with a nearly 50% increase in cortical gray matter (10), a nearly threefold increase in myelinated white matter (10), and increasing neuronal and gyral differentiation (11). In a large study of third grade children, math and reading scores progressively increased from 37 to 40 weeks (12). In children born at 34 to 36 weeks there is an increased incidence of a variety of abnormalities of intellectual and neurologic function (12), and with greater degrees of prematurity, such deficits are increasingly common.

A further risk of twin pregnancies is the impact of complications on families. Birth of a severely handicapped child can be devastating, and siblings of a disabled child can be psychologically affected (13). Mothers of twins have a higher risk of depression, and divorce is more common (14, 15).

It has been suggested eSET is not appropriate in older women or younger women facing a progressive decrease in ovarian function, and that twins are a desirable outcome to help them complete their family. However, twins will significantly increase the risk of maternal complications in older women (16). An alternative is to undergo two or more banking cycles to store multiple euploid embryos while fertility is higher, which will also reduce miscarriage and its associated delays and psychological trauma. DET may decrease the chance of later pregnancies if only one of the embryos implants, because a further cycle will be delayed until after delivery.

Insurance companies in the U.S. are increasingly encouraging eSET by choosing referral centers based on the number of embryos transferred, due to high costs of providing medical care to preterm babies (14), further magnified now that more extremely premature babies are surviving (14). Lifetime expenses of medical care for resulting disabilities further increase costs.



Pro 2. Anja Pinborg, M.D., D.M.Sc.

IVF twin rates have been steadily decreasing worldwide from above 30% to less than 10% more recently. Live birth rates per started cycle have remained unchanged (17). Simultaneously decreases in preterm birth and perinatal mortality rates have been observed, with the steepest decline in countries pioneering

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be transferred for a favorable prognosis couple (with the exception of euploid embryos) is 1, ≤ 2 , and ≤ 3 for patients < 37 , 38–40, and 41–42 years of age, respectively (38).

A debate over the relative utility of eSET and DET policies need not resolve the simpler question, that is, whether or not twin pregnancies constitute an undesirable outcome of either assisted or unassisted conception. All else being equal, twin pregnancies are best avoided (41–45). The mono-ovulatory uniparous species that is humanity is ill-designed to accommodate multiple intrauterine offspring (46). What is under discussion herein is the rationalization of those twin pregnancies that are the product of a discretionary DET policy that is selectively applied (39, 40).

A uniform eSET policy is hardly without shortcomings. In the eyes of DET-eligible patients, it may be considered as needlessly effort and cost intensive at best, and potentially compromising to their chance of success at worst. Although the total cost-effectiveness into the neonatal period of eSET can be questioned when compared to the costs of DET because of the higher success rate of DET (47, 48), when DET was compared to two sequential SETs (as occurs with cryopreservation of the additional embryo), the total costs decreased from 581 to 386 million dollars per 10,000 births (49). However, from purely a patient rather than societal perspective, infertility treatment expenses are out of the couple's pockets, whereas pregnancy and neonatal costs come out of a different pocket (medical insurance). A uniform eSET policy may also be regarded as ill-suited for couples who prefer an accelerated approach to family building, particularly in the presence of age-dependent decrements in ovarian function. Other examples include those afflicted with age-inappropriate ovarian function, those who may have previously experienced an IVF failure, or those who lack the psychological and/or financial means to embark on what could prove to be a long stretch of uncertainty. As has been repeatedly shown, the success rates of DETs are superior to those of eSETs (48, 50, 51). Although the cumulative live birth rate of sequential eSETs is comparable if not superior to that effected by a single DET in the context of the young patient (50, 51), for older couples or for those with specific pathologies, that may not be the case. Furthermore, for couples desiring more than one or two offspring, a more accelerated approach may be more in concert with those desires. It is here that all-important patient autonomy must be preserved with eSETs not being mandated for lower prognosis couples by providers, payers nor by national guidelines or regulations.

In 2015, the national twin birth rate declined from 33.9 to 33.5 per 1,000 total births (52) and the contribution of IVF to the national twin birth rate also declined from 15.6 to 14.5% (53). Still, 11% and 59% of the twins born in 2015 were very preterm (under 32 weeks) and preterm (under 37 weeks), respectively (52). In addition, 10 and 55% of the twins born were characterized as very low birthweight ($< 1,500$ g) and low birthweight ($< 2,500$ g, respectively (52). Continued vigilance and measures to reduce these complications are clearly required. As embryo implantation rates and insurance coverage for IVF continue to

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broader application of SET, such as Sweden and Finland (18). Risks in twin pregnancies are up to ten-fold higher and still birth occurs two to three-fold more often compared to singleton pregnancies (19). Twin births should be compared to two sequential singleton births, as the second birth is not associated with the higher obstetrical risks of nulliparity. Risks of IVF twins substantially exceed the risks of two IVF singleton births (4). The prevalence of neurodevelopmental disability including cerebral palsy is higher in twins than singletons in population-based studies (20). In ART singletons of <32 weeks of gestational age the prevalence of cerebral palsy was doubled compared with spontaneously conceived singletons, but for ART twins the odds of CP was significantly higher than for ART singletons (21). By adjusting for preterm birth, risks for twins diminish, however preterm birth should be considered as a mediator and not a confounder in the relationship between ART twins and neurodevelopmental outcomes. The risk of preterm birth is increased in ART singleton pregnancies resulting from a vanishing twin pregnancy and the later in pregnancy the spontaneous reduction occurs the higher the risk of cerebral palsy (22). Thus, consequences of DET are not only observed in twin pregnancies but also in singletons pregnancies with spontaneous reduction, even if the reduction occurs before week 7-8 (22). Data suggesting that CP is increased in singleton pregnancies with transfer of more than one embryo, but not with SET (21, 23, 24) should be reproduced in larger studies. If further validated, that observation alone argues very strongly for SET. Maternal mortality is also higher in twin IVF pregnancies (25, 26).

Because of the persistent occurrence of twins after DET, it has been suggested to expand eSET policy to include women under age 38 until their third cycle and for cryopreservation cycles (27). The ability to further reduce IVF twin rates is influenced by local regulations and costs of IVF treatment. In Denmark for couples under age 40, up to three IVF cycles, including surplus FET cycles, are fully reimbursed, and costs for medication are partly reimbursed above a self-payment of 1000 dollars. A guideline from the Danish Fertility Society in 2015 established a policy aimed at reducing the twin rate to 5-8%. It was recommended that single embryo transfer should be routine except in cases with low prognosis (e.g. women \geq 40 years of age, more than 4 unsuccessful IVF embryo transfers, or decreased embryo quality). This effort reduced the twin birth rate to 5% in 2016, with the majority of clinics following the guideline without lowering their overall pregnancy rates. Obstetric risks are even greater in ageing women, therefore DET should only be considered after failed treatment cycles and with lower quality embryos. Similar progress is more difficult to achieve in locations where the costs of fertility care are borne by the couple themselves.

Patients' perceptions and decisions regarding eSET are dependent on the level of information as well as the attitude and commitment of their physicians and ancillary personnel. Provided they are adequately educated regarding the risks of a twin pregnancy to the mother and her offspring, most couples

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increase, at least some of the mitigating circumstances leading couples to choose DET will abate and any excess risks and costs further debated herein are certain to also decline (54).



Con 2. Norbert Gleicher, M.D.

Two studies have suggested clinically relevant increases in maternal and neonatal risks with IVF twins over two consecutive IVF singleton pregnancies (4, 55). The Swedish study claimed to have demonstrated "dramatically" higher maternal and neonatal risks (4). Cesarean sections were increased (odds ratio [OR] 4.19, 95% confidence interval [CI] 3.32-5.29), as were risks for premature rupture of membranes (OR 8.43, 95% CI 4.86-14.63) and preeclampsia (OR 2.64, 95% CI 1.81-3.86). Risks of placenta previa were, however, reduced (OR 0.37, 95% CI 0.17-0.81), and there were no differences noted in gestational diabetes, other maternal morbidities or maternal mortality. Neonatal risks were higher for sepsis (OR 2.31, 95% CI 1.29-4.13), respiratory complications (OR 4.92, 95% CI 3.68-6.58) and jaundice (OR 5.03, 95% CI 3.77-6.70); but, most importantly, Apgar scores below 7, perinatal and first-year mortalities as well as congenital abnormalities did not differ. La Sala et al. (55) also concluded that twin pregnancies gave rise to more complications. They, however, reached this conclusion without demonstrating any differences in Apgar scores, neonatal intensive care unit admissions, perinatal mortality, intrauterine fetal demises and neonatal deaths. A more balanced conclusion would be that twin pregnancies appear associated with mildly increased maternal and neonatal complications than two consecutive singleton pregnancies. These reports call into question how clinically relevant these differences in risk are.

Any risks must always be balanced against benefits. The improved pregnancy chance of DET in comparison to eSET has remained undisputed (50). Although some reports, as mentioned previously, have suggested equal or better success with two consecutive SETs, at a minimum successful live birth/s are delayed and intervening uterine pathology could preclude success in an individual patient. It is irresponsible to suggest to infertility patients that following a first successful IVF cycle they can expect a second equally successful cycle. Even with the newest cryopreservation techniques using vitrification of embryos there is a chance of failure of embryos to survive freezing and warming (reported as 3-14%) (56, 57). Although some will speculate that embryos failing to survive cryopreservation lack the capacity to implant, couples must be informed that deferred transfer may carry some risk to capable embryos.

A further important issue is cost. Most comparisons have relied on modelling and, therefore, on often unsupported assumptions. Moreover, not a single cost-effectiveness study

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will prefer single embryo transfer, only very rarely asking for DET. Couples should be reassured that similar cumulative live birth rates can be obtained by sequential SET compared to double embryo transfer (4–6). In most Nordic settings at the initial visit couples are informed about single embryo policy, the risks of twin pregnancies and success rates using sequential fresh and frozen SET cycles.



Pro 3. Brad Van Voorhis, M.D.

In the absence of counselling, couples commonly desire twins. In one study, at intake, 30% of infertility patients listed a twin, triplet, or quadruplet pregnancy as their most desired outcome. Associated factors were nulliparity, lower family income, younger patient age, and limited knowledge of medical complications

of twin pregnancies (28). Younger nulliparas may underestimate the challenges of raising twins. Those with a lower income may wish to achieve their ideal family size with less cost. In a further study, 29% of couples presenting for IVF listed twins as their most desired treatment outcome, their most common reason being to reach an ideal family size more quickly (29).

Education can alter patient desire for twins (29, 30). Using written and verbal communication, couples were educated about the health risks of twins to pregnant women, their fetuses and offspring. Fewer patients ranked twins as their most desired outcome following education (14% versus 29%, $P < .001$). Nevertheless, patients often would still choose double embryo transfer if they perceived success to be as little as 5% greater (29, 31–33).

Education must also focus on cumulative pregnancy rates. Although eSET results in a small but significant decrease in achieving pregnancy, the cumulative pregnancy rate with two sequential SET's is at least equal to that achieved with DET (4–6). With modern embryo freezing techniques, improved embryo selection and accumulating evidence about the adverse effects of ovarian stimulation on endometrial receptivity, our focus should be on cumulative outcomes. Costs of an eSET strategy pale in comparison to those borne by patients and the healthcare system from multiple gestation pregnancies and newborn care.

In one study an educational DVD increased acceptance of eSET more than a brochure (34). Particularly effective were patient testimonials about their experience and resulting stress with premature twin deliveries. Decision aids graphically demonstrating risks of adverse outcomes were also useful (35). Recently, Centers for Disease Control and Prevention and SART partnered to distribute a patient education sheet summarizing outcomes data from singleton and multiple gestation pregnancies following IVF. SART has created a pre-

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has considered life-long earning potentials of offspring. By covering in their models only pregnancy, delivery, and neonatal periods, all of these studies created a one-sided balance sheet of only expenses, without consideration of income for society.

The Canadian province of Québec initiated a government-sponsored insurance program for IVF, which traded establishment of the program for a commitment by the IVF community toward eSET. Significant reductions in twin pregnancy rates in the province were presented as an overwhelming success of the program (58). What authors and government bureaucracy, however, did not consider in their initial program assessment was the fact that Québec lost 26.2% of its IVF pregnancies/births because of lower eSET than DET rates and a large part of their second child birth rate resulting from twins. Combined, the province lost roughly a third (33.1%) of their annual IVF births (59). The program was terminated because of cost-concerns.

The last 10 years of available data from Japan and Australia/New Zealand, the two regions of the world where eSET utilization has been increasing the most, point out additional consequences of an aggressive eSET policy. Japan over that time period lost two-thirds of the country's live births, while tripling cycle starts. Australia/New Zealand demonstrated a similar interplay between live birth rates and cycle starts (60). Despite having highly sophisticated levels of reproductive biology research, these two regions of the world produced over this decade by far lowest live birth rates anywhere in the industrialized world (60). Considering how much infertile women prioritize establishment of pregnancy over almost all other considerations (61), such practice cannot be viewed as "patient-friendly" and/or clinically appropriate.



Con 3. Jean Parinaud, M.D., Ph.D.

A majority of couples undergoing infertility treatments consider twins the best outcome (28, 33, 62–67). Whatever their geographic origin, U.S., Europe, Australia, or Africa, more than 50% prefer to have twins, because they want their children to have a sibling, they have a positive attitude towards having twins, they want to have as few treatments as possible (64, 68), they have long-time infertility (65) and they have fears regarding the female partner's age (64). Being nulliparous and desiring to limit infertility treatment costs are also reasons to prefer twins (28, 66). In one study, neither the woman's age nor the degree of education had an influence on the desire for twins (66).

The attitude of patients toward a twin pregnancy can be influenced greatly by the extent of information given by the medical team regarding risks. However, when three scenarios of risks were presented to patients (low, medium and high), only the highest risk changed their desire for twins (62, 63).

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dictor of IVF treatment outcomes (www.SART.org) which allows patients to enter their own demographic and clinical information and compare individualized estimates of cumulative and multiple gestation pregnancy rates with DET vs. sequential SET. This powerful tool allows patients to see that equal or even superior pregnancy rates can be achieved in their particular situation with sequential single embryo transfers.

Some patients will still insist on DET. Physicians and other healthcare providers should follow the highest standards of ethical clinical practice. Although respect for patient autonomy is an important bioethical principle, so too is the principle of non-maleficence ('do no harm') and the right of conscientious practice for physicians. Deferring to patient autonomy inappropriately abrogates the important moral and ethical responsibilities of the physician by making physicians mere technicians or vendors of healthcare goods (36, 37). The American Society for Reproductive Medicine/Society for Assisted Reproductive Technology practice committee recently revised the embryo transfer guidelines to unambiguously call for transfer of a single embryo in good prognosis patients (38).

One way to strengthen an eSET program is to inform the patient at their initial visit that your clinic's policy is to follow professional embryo transfer practice guidelines to give them the best and safest outcomes of treatment. This respects patient autonomy by providing full information, opening up discussion, and allowing patients who disagree to seek care elsewhere. These discussions must take place long before the emotionally charged day of embryo transfer. We have found that patients are highly receptive to an eSET policy when they appreciate the clinic's commitment to achieving both a high pregnancy rate and optimal maternal and neonatal outcomes. Healthy singleton babies should be the expectation and seldom the exception.

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The way information was presented (brochure, interview with obstetricians, embryologists or nurses, DVD) had no effect on patients' attitudes (33, 34). Thus, it's the position of the medical team toward multiple pregnancy which is the most important thing that influences patients' preferences. Dramatizing the outcome of twin pregnancies appears to be the best way for convincing patients to accept eSETs. The number of previous IVF attempts also has a great impact since, after one IVF failure, 41% of patients who preferred singletons before the first attempt turn into a preference for twins (67). Personal experience of having twins is very positive (85% of IVF-twin mothers preferred twins, while only 38% of IVF-singleton mothers preferred singleton) (69). Twin pregnancies are well accepted and even wished by patients as an acceptable risk to increase the chances of parenthood. Indeed, while the use of eSET in good prognostic patients maintains good pregnancy rates, its application to all patients results in lower pregnancy success (70). Therefore a universal attitude toward the number of embryos to be transferred is difficult to accept, and the choice must be made by patients and physicians according to the patients' desires, the chances of success and the individual's risk of a twin pregnancy as a function of patient characteristics and medical history (40).

Many factors can influence implantation rates such as the woman's age, ovarian response to stimulation, rank of attempt or embryo morphology and developmental kinetics. Integration of these parameters into a global score may help in the decision to transfer of 1 or more embryos. Gatimel et al. (71) calculated a score including age, ovarian response, rank of attempt and number and morphology of embryos which allowed prediction of early embryo implantation over a range of 5 to 28%. Evaluation of embryo quality through time-lapse observation holds promise, although its use remains controversial. A Cochrane review of randomized controlled studies showed an increase in clinical pregnancy rate which was not statistically significant (72). Since this technique needs a sizeable investment, more data must be available before its routine use. Genetic screening of polar body (73) or embryos (74) according to some authorities allows detection of euploid embryos with an increased potential for development. However, that contention is controversial and its use will also remain restricted due to expense. Therefore, the transfer of more than 1 embryo is still the best way to improve results in patients with moderate or low chances of success, while taking a moderate risk of twins.

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