

Mistaken advocacy against twin pregnancies following IVF

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Abstract

Purpose A recent publication by Swedish Colleagues in *Fertility & Sterility* for the first time, statistically correctly, attempted to assess risks of twin IVF pregnancies in comparison to two consecutive singleton IVF pregnancies. Historic comparisons have been statistically incorrect, comparing risks of one twin to one singleton pregnancy. We here analyze data and conclusions presented in this Swedish study.

Methods We reviewed the manuscript by Sazonova et al. (*Fertil Steril*, 2013) (doi: 10.1016/j.fertnstert.2012.11.023).

Results Based on incorrect statistical methodology, twins after in vitro fertilization (IVF) have come under attack as “adverse” outcomes. Above noted study recently, for the first time, correctly compared one twin to two consecutive singleton pregnancies. Investigators, however, in our opinion interpreted their own data incorrectly by claiming “dramatically” higher maternal and neonatal risks in twin pregnancies. Our interpretation of reported data, indeed, in contrast suggests surprisingly minor differences in observed twin-risks. Moreover, such minor risk increases do not offer

adequate compensatory benefits for significantly lower pregnancy chances in first IVF cycles with eSET in comparison to two-embryo transfers (2-ET).

Conclusions As significantly higher maternal and neonatal risks of twin IVF pregnancies represent the principal rationale for eSET, the Swedish study actually suggests that eSET offers neither patient-friendly nor cost-effective treatment options for IVF, except where patients object to twins or have medical contraindications. The need for a second pregnancy to achieve equal outcome (2 children), resulting treatment delays, increased efforts and costs, in absence of any guarantees that a second successful singleton pregnancy/delivery will ever be accomplished, invalidates eSET as a routine procedure.

Keywords IVF/ICSI · Maternal complications · Neonatal complications · Cost-effectiveness · Singleton pregnancy · Twin pregnancy

Capsule Acknowledging that most of the literature, defining outcome risks of IVF-twins, utilized statistically inappropriate data sets, a recently published study in *Fertility & Sterility*, correctly compared risks of one IVF twin pregnancy to risks of two consecutive singleton pregnancies. The authors, however, incorrectly interpreted results of their own study by concluding that allegedly observed lower risks of two consecutive singleton deliveries support increasing utilization of elective single embryo transfers (eSET). This communication offers an opposing interpretation of their data.

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Demonstrating that even cautious ovulation induction leads to unacceptable high-order multiple pregnancy rates, we in 2000 suggested that IVF offers an opportunity to reduce high order multiples by limiting the number of transferred embryos [1]. Ovarian hyperstimulation in non-IVF cycles, however, has remained responsible for a large majority of fertility treatment-associated multiple births [2, 3]. Paradoxically, IVF, and not medical ovulation induction, has, however, become a primary target of criticism and interventions to reduce multiple births, even twin pregnancies [4–6].

The history of eSET

Controlling multiple pregnancies by limiting transferred embryos quickly gained popularity in association with IVF after Templeton and Morris demonstrated that, in favorable patients, transfer of more than two embryos no longer

increased pregnancy chances but significantly raised high-order multiple risks [7]. Since avoidance of high-order multiples reduces obstetric/neonatal risks, they established superiority of 2-embryo (2ET) over, then still widely popular 3- (or more) embryo transfers.

When Finnish investigators then, however, proposed to expand the argument, favoring elective single-embryo transfer (eSET) over 2ET, statistical considerations differed significantly [4]. While Templeton and Morris' paradigm had not affected pregnancy chances, switching from 2ET to eSET significantly did [8]. In proposing the switch to eSET, the Finnish investigators in addition overlooked that risk differences (i.e., differences in adverse outcomes) greatly varied between both paradigms (a very important fact we will be returning to): Risk differences between twin and singleton pregnancies were significantly smaller than between high order multiples and twin pregnancies [9]. With risk differences varying, risk/benefit considerations, of course, also should vary.

In Templeton and Morris' paradigm comparatively greater risks were avoided to mother and offspring by avoiding high order multiples, with no reduction in pregnancy chances. Since risks of twins are so much lower than of higher order multiples, the new eSET paradigm offered much smaller risk reductions, and, in addition, resulted in significant declines in pregnancy chances. These differences raise the question whether a comparatively smaller risk reduction by eSET by avoiding twins offers appropriate compensatory benefits for lost pregnancy chances from eSET.

Blatant statistical errors

In answering this question, blatantly obvious statistical method errors become apparent in how alleged benefits of eSET have historically been assessed in the literature. The increasingly popular viewpoint that twin pregnancies represent "adverse" IVF treatment outcomes [10, 11], therefore, was questioned [12].

While outcome data should not be transferred between treatment paradigms and populations, this is exactly what happened, mostly unrecognized by peer review, and largely uncritically accepted by reproductive endocrinology, maternal-fetal medicine and neonatology specialties. Retrospective obstetrical outcome data, comparing outcomes of twin pregnancies (resulting in delivery of two children) with outcomes of singleton pregnancies (resulting in delivery of one child) were, uncritically applied to infertility practice, which, of course, represents a prospective treatment paradigm, at least theoretically, targeting delivery of one or two children as desired goals.

In a retrospective paradigm, twin gestations, statistically correctly, carry increased risks. Assuming that a fertility

patient wishes to complete her family with two or more children, the treating physician here, however, faces the question what represents the safest, quickest and least costly way to achieve delivery of two children? Unrealistically assuming that twin pregnancies can be commanded, the fertility specialist can, therefore, either strive for one twin or two consecutive singleton gestations.

The appropriate statistical comparison of risks (and costs) for such a prospective fertility paradigm is, therefore, between one twin pregnancy and *two* singleton pregnancies, significantly differing from prior discussed retrospective obstetrical paradigm, comparing one twin to *one* singleton pregnancy. Obstetrical risk comparisons, therefore, are statistically inappropriate for risk assessments in association with IVF, a point we made before [12].

Relevant studies

Building on our comments, René Frydman's group in Paris retrospectively investigated in their data base pregnancy outcomes of women who delivered twins after IVF with those who delivered two consecutive singleton pregnancies. They concluded that, assessing outcome risks in this way, and considering outcome risk differences observed, twin pregnancies represented an entirely reasonable option for IVF patients (Lemazou F, personal communication, Paris, France 2011). These data, however, so far have not been published.

The literature suggests that obstetrical outcome risk of IVF twins may, indeed, be exaggerated because they vary from those of spontaneously conceived twins. Helmerhorst et al. reported in a review of the literature that IVF twins experience approximately 40 % lower perinatal outcome risks than spontaneous twins. In contrast, IVF singletons demonstrated higher outcome risks than spontaneously conceived singleton pregnancies [13].

It, thus, appears that correct risk comparisons in a prospective infertility paradigm, therefore, have to compare outcome risks of one twin to *two* consecutive singleton pregnancies and, in addition, should be adjusted for lower outcome risks for IVF twins and higher risks for IVF singletons if obstetrical risk data are utilized in risk comparisons between singleton and twin pregnancies. When this is done correctly, we reported already in 2009 that risk profiles for IVF twins and two consecutive IVF singletons can be assumed to be very similar [12].

We reached this conclusion, however, only based on above noted analysis by Helmerhorst et al. [13], and data from the obstetrical literature, requiring statistical adjustments. Recognizing the obvious statistical shortcomings of currently available literature on the subject, Swedish investigators now published in *Fertility & Sterility* an important

first nationwide study of only IVF patients, comparing maternal and neonatal outcomes in those with one twin pregnancy to women with two consecutive singleton pregnancies [14]. This study, therefore, had the potential of, once and forever, answering the question whether IVF twins really carry excessive risk. Unfortunately, the study suffers from major shortcoming, not the least a rather remarkable misinterpretation of presented data. Because *Fertility & Sterility* was not interested in a detailed critique of the study, such a critique is presented here.

A general critique of the Swedish study

While the study by Sazonova et al., laudably, presented a correct prospective statistical infertility paradigm of comparing one twin to two singleton pregnancies, it does not mimic the clinical circumstances of an infertility patient, consciously choosing consecutive singleton pregnancies. It, therefore, for example, does not establish how many infertile women will not conceive a second pregnancy after eSET. Nevertheless, the study represents an important milestone in recognizing that past risk assessments were statistically flawed, and pointing accumulation of new evidence into the right direction. Since presumed risks of twin pregnancies represent the only rational for worldwide eSET recommendations, this Swedish study, therefore, indeed carries significant potential importance.

The study reports on 1,982 children to 991 mothers in twin pregnancies after 2-ET, and on 921 mothers giving birth to 1,842 children in two consecutive singleton pregnancies. Somewhat surprising, the rate of maternal as well as neonatal complications in second singleton pregnancies was significantly lower than in first singleton pregnancies. Since mothers in second singleton pregnancies by definition should be older, they, actually, should demonstrate increased maternal and fetal/neonatal risks [15]. Demonstrating a convincing trend into the opposite direction, the authors speculate that these unexpected findings may be consequence of lower outcome risks in multiparous women.

As the authors note, mothers of IVF twins were older. They, however, do not raise the possibility that this observation, alone, may suggest potential biases based on maternal age in embryo numbers transferred, as older women are more desirous of twin pregnancies [16]. They also leave unmentioned that 96.3 % of twin-mothers and a full 99.0 % of mothers of consecutive singletons were under age 40, though ages of singleton mothers at each of their two pregnancies remain undefined. The study population, therefore, undoubtedly, was unusually young.

A first point to be made about the study by Sazonova et al. is, therefore, that significant patient selection biases

cannot be ruled out. Indeed, whatever relevance the study ultimately will be assigned, it relates, very obviously, only to relatively young patients under age 40. It is, however, based on age and length of infertility, disproportionately the desire of older women to have twins [16].

Risk differences between one twin and two singleton pregnancies

Maternal risks differ to quite minor degrees between the two groups: Higher risks for twin deliveries included placental abruption (adjusted OR 1.30), cesarean section (adjusted OR 4.19) and preterm premature rupture of membranes (adjusted OR 8.43). The risk of placenta previa was, however, in contrast, lower with twin delivery (adjusted OR 0.37). Remarkably, Preeclampsia and gestational diabetes prevalence did not differ between both study groups, and neither did maternal mortality.

Maybe even more remarkable were the relatively minor differences in neonatal morbidity: Twin deliveries only demonstrated increased respiratory complications (adjusted OR 4.92) and jaundice (adjusted OR 5.03), both very obviously the consequence of increased prematurity; but neither perinatal mortality, Apgar scores below 7 at 5 min, mortality in the first year of children's lives or congenital malformations differed between the two study groups.

In other words, what obstetrical practice widely refers to as mild morbidity was, indeed, increased in association with twin deliveries but all adverse perinatal/neonatal factors, associated with long-term morbidity and/or mortality demonstrated absolutely no outcome differences between the two study groups. Yet, quite surprisingly, the authors concluded that their study demonstrated “dramatically better maternal and neonatal outcomes” if they underwent two consecutive singleton rather than one twin pregnancy, and that their “results, therefore, support eSET to minimize the risks associated with twin pregnancies.”

As above presented summary of maternal and neonatal outcomes indisputably demonstrates, both conclusions are completely unsupported by the authors' own data. We, therefore, respectfully disagree with their conclusions: As already noted, whatever conclusions are reached, they can be applied only to relatively young patients under age 40 years. More importantly, however, without minimizing observed increases in short-term morbidity in association with twin pregnancies, these risks have to be considered rather minor, easily, and at rather small costs, manageable in a modern health care system. Sazonova et al., indeed, demonstrate how relatively safe IVF twin deliveries have become in a well run medical system like the Swedish health care system. The study demonstrated, after all, no differences in Apgar scores, perinatal/postnatal mortality or

congenital abnormalities between the two patient groups. How the authors, therefore, can conclude to have demonstrated “dramatically better maternal and neonatal outcomes’ is unclear.

Conclusions

Increased mild neonatal morbidity in association with twin deliveries, undoubtedly, increases neonatal health care costs. Such increased costs are, however, more than compensated for by cost savings from avoidance of additional infertility treatments and especially by the lifelong economic contributions of second twins to society. Based on economic data from The Netherlands, Evers calculated that every IVF-offspring contributes a lifelong economic net of €238,000 (\$310,000) to the country’s Gross National Product. He, therefore, concluded that, theoretically, up to that sum could be spent on a successful IVF cycle without society incurring a net loss (International Federation of Fertility Societies [17]).

Recent experience demonstrated that, by reducing pregnancy chances and eliminating second twins, a rigorous eSET program eliminates approximately one-third of potential newborns [18]. National economic interests, therefore, support neither Sazonova et al’s study conclusions, nor the concept of eSET, unless patients have medical contraindications to twin pregnancies or simply do not wish to conceive twins.

Like other proponents of eSET, Sazonova et al. build on the argument that cumulative pregnancy chances from two consecutive, one fresh and one frozen-thawed, eSET cycles are almost equal to those of a single 2ET [8]. Considering the rather minor increases in short-term morbidity observed with twins in their study, why should patients go through two treatment cycles and two pregnancies, when one may be enough for, practically, almost identical outcomes? Moreover, which fertility center can ever guarantee that, after giving birth to a singleton, a patient will successfully conceive and deliver a second time? Not every frozen embryo survives thawing; fertility potential declines with advancing age; and circumstances, including social circumstances, do not remain static over time.

Sazonova et al. also cannot tell us how many fertility patients will fail to ever achieve a second pregnancy, how long it took those who were successful to conceive, and what the additional costs would have been for all of those successful and futile attempts. They in their study, however, paradoxically, present the, likely, best available evidence so far that even in younger infertile women a twin pregnancy cannot be considered an adverse outcome. Indeed, medical contraindications aside, the older the patient, the more likely it should be viewed as a very favorable outcome. Sound

additional arguments in favor of twin pregnancies can also be made based on patient rights to self determination and patient preferences [16, 19].

The concept of eSET offers in our opinion a worrisome example of how an obviously incorrect statistical paradigm can enter routine medical practice, and become basis for guidelines, and even legislative interventions (Gleicher [20]). Sazonova et al. deserve credit for bringing attention to this fact. It, however, appears time to go beyond this point, and end the “political correctness” that has fed the increasing popularity of eSET. Evidence does not support eSET!

The March of Dimes recently identified multiple births after fertility treatment as a new subject of interest for the organization, and on June 20–21, 2012, in collaboration with the Hastings Center, organized a Stakeholder Workshop. A detailed report should be forthcoming in the near future. Hopefully, it will consider here outlined fundamental flaws in current risk assessments, and, thereby, help redirect practice patterns away from “political correctness” towards evidence-based practice.

Conflict statement NG and DHB have no conflicts to declare with respect to here presented manuscript. They received research and grant support, travel funds and speaker honoraria from various pharmaceutical and medical device companies, none, however, related to here presented topics. NG and DHB are listed as inventors on two already awarded (November 10, 2009; #7615544 and November 29, 2011; #8067400) and other still pending United States patents, claiming beneficial effects on diminished ovarian reserve (DOR) and embryo ploidy from dehydroepiandrosterone (DHEA) or from other androgen supplementations. NG is owner of CHR, where this research was conducted, and is a shareholder in Fertility Nutraceuticals LLC, a producer of fertility nutraceuticals. NG and DHB receive patent royalties from the company. Both are also listed as co-inventors on a number of pending United States patents, claiming diagnostic relevance for the assessment of triple CGG repeats on the *FMR1* gene in determining risk towards DOR and related issues.

All patent applications filed by researchers at CHR are 50 % owned by CHR and 50 % by the investigators who did the research that led to the application. A full list of all patent information can be provided on request.

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