Twin pregnancy, contrary to consensus, is a desirable outcome in infertility

Norbert Gleicher, M.D., a,b,c and David Barad, M.D., M.S., a,b,d

a The Center for Human Reproduction, New York; b Foundation for Reproductive Medicine, New York, New York; c Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut; and d Departments of Epidemiology and Social Medicine and Obstetrics, Gynecology and Women’s Health, Albert Einstein College of Medicine, Bronx, New York

Objective: To determine whether the worldwide consensus that twin pregnancy after fertility treatment represents an adverse outcome to be avoided is correct.

Design: Literature search via PubMed and MEDLINE, going back to 1990.

Setting: Academically affiliated private fertility center.

Patient(s): Mothers and offspring in singleton and twin pregnancies.

Intervention(s): None.

Main Outcome Measure(s): Maternal and perinatal/neonatal risks as well as cost considerations for singleton versus twin pregnancies.

Result(s): Most risk assessments of twin pregnancies after fertility treatment have used spontaneous conceptions data, which reflect different treatment paradigms and outcome benefits from pregnancies after fertility treatments. In vitro fertilization (IVF) twins demonstrate approximately 40% lower outcome risks than spontaneous twin conceptions. Most risk assessments in the literature are calculated with pregnancy as the primary outcome, but in a fertility-treatment paradigm where patients want more than one child the statistically correct risk assessment should refer to born children as the primary reference. If published data are corrected accordingly to achieve statistical commonality of outcome (i.e., one child in singleton versus two children in twins), twin pregnancies no longer demonstrate a significantly increased risk profile and/or cost for mothers or individual offspring.

Conclusion(s): For infertile patients who want more than one child, twin deliveries represent a favorable and cost-effective treatment outcome that should be encouraged, in contrast to the current medical consensus. (Fertil Steril 2008; –: –: –. 2008 by American Society for Reproductive Medicine.)

Key Words: Twins, twin pregnancy, multiple births, in vitro fertilization, infertility, fertility treatment, adverse outcomes

In recent years, multiple births have skyrocketed, with most of the increase attributable to infertility treatment (1–3). Because multiple pregnancies increase the risk to mothers and offspring, this development has caused worldwide concern (4, 5). Risks, of course, further increase as the order of multiples rises (6, 7). Thus, initial efforts have concentrated on reducing high order multiples when the potential of risk is the greatest (5, 8, 9). More recently, however, aggressive worldwide efforts have turned toward reducing the prevalence of twin pregnancies because they represent a large majority of multiple births after fertility therapy (10, 11). These efforts, originally initiated mostly by European investigators, have resulted in the concept of single-embryo transfer for in vitro fertilization (IVF), which has achieved wide popularity and has been aggressively communicated to the public (12–15).

A principal argument in favor of reducing twin pregnancies has been medicine’s primary ethical charge to do no harm. Because singletons are widely assumed to be safer than twin deliveries, the argument has been that fertility treatments should (even at the possible expense of reducing pregnancy chance) mount every possible effort to avoid the added risks of twins. This argument is, however, flawed and should, therefore, no longer be conveyed to the public. As this article will demonstrate, for most infertility patients, single-embryo transfer strategies are inappropriate.

MATERIALS AND METHODS

Using MEDLINE and PubMed, we performed a literature search retroactive to 1990 that addressed risk and cost
comparisons between singleton and twin deliveries. The following key words were used: twins, twin pregnancies, twinning, multiple births, infertility, infertility treatment, in vitro fertilization (IVF), assisted reproductive technologies (ART), single embryo transfer, perinatal mortality, perinatal morbidity, maternal mortality, maternal morbidity, prematurity, pregnancy complications, cost, and cost effectiveness.

**Historical Perspective**

Most multiple births after fertility treatments are not a consequence of IVF but of other fertility therapies (3, 8). Indeed, IVF represents the only fertility treatment that offers a reasonable degree of control over the multiple pregnancy risk by allowing the number of embryos transferred into the uterus to be determined (8). This recognition led to the concept of age-specific and ovarian function–specific embryo transfer criteria in attempts to control the risk of multiple births with IVF (16).

The logic of such criteria seemed obvious when two-embryo transfer (2-ET) was demonstrated to achieve identical pregnancy rates to the higher-order transfer numbers in properly selected women (17, 18). Once outcomes were comparable, there was no longer an indication to even consider procedures with potentially higher risk profiles. However, outcome was not identical when single-embryo transfer subsequently was compared with 2-ET and was found to result in lower pregnancy rates (though, of course, also significantly lower twinning) (19–21).

In view of an allegedly higher risk profile of twin pregnancies, proponents of single-embryo transfer nevertheless argued that lower risk profiles for singleton pregnancies made lower pregnancy rates acceptable; diminished pregnancy potential can, after all, be made up with more interventions (i.e., more embryo transfers or more IVF cycles). They overlooked, however, that with single-embryos transfer any established pregnancy will, in principle, always be a singleton pregnancy, resulting in birth of one child, whereas every twin pregnancies gives birth to two children. To equalize outcomes by number of children (and not by pregnancy), every woman who initially managed to deliver a singleton will have to undergo a second (singleton) pregnancy experience.

**Risk/Benefit**

Because risk/benefit evaluations represent the basis of all medical practice, they also should apply to infertility patients. The principal desired benefit from fertility treatment is relatively simple to define: it is not clinical pregnancy but rather the birth of (healthy) children. Indeed, it is usually not just the birth of a single child because a majority of women want more than one child. Specific data on this topic are mostly lacking, but it is possible to extrapolate from related data sets: over two thirds, for example, prefer twins over singletons if given the choice, and a surprising minority even wants triplets (22). Such a conclusion also was supported by two recent nonscientific Internet polls (23, 24), which concluded that only 11% of 140,000 and 6% of 18,000 respondents wanted a single child.

Number of desired children represents a very important consideration in determining the risk/benefit of fertility therapy accurately. If a hypothetical couple initiates fertility treatment with the goal of having two (or more) children, their maximal potential benefit from treatment would, of course, be the delivery of two (healthy) children in as short a time frame as possible (and, as we shall further discuss, at the lowest possible cost). Their risks (and costs) are then rather simple to assess as defined by the cumulative risks (and costs) of all pregnancies/deliveries (and treatments) required to deliver two children. In other words, if this hypothetical couple had two children as the result of a single twin pregnancy, their risks (and costs) would be those of this one twin pregnancy. If, however, two singleton pregnancies were required to deliver two children, their overall risks (and costs) would be defined by the cumulative risks (and costs) of those two pregnancies.

The correct statistical conclusion from all of this is, therefore, that an outright comparison of risk (and cost) between a singleton and a twin pregnancy, with pregnancy as the reference point, is for infertility patients (in contrast to obstetric patients) nonsensical. A corrected statistical comparison requires the acknowledgment that after a singleton delivery a woman (who wants at least two offspring) will need further infertility treatments (though even such treatment can never guarantee a successful second pregnancy) and at least one additional pregnancy (baring miscarriages) to reach the desired outcome of two delivered children. Any second singleton pregnancy will then double the singleton risks (and costs) of her first pregnancy without guaranteeing a second successful delivery.

Mathematically, this means that, if the risk for one offspring in a singleton pregnancy is $x$, the combined risk for two offspring in two singleton pregnancies will be $2x$. The principal question that now arises is whether this $2x$ risk does or does not exceed the risk of one twin delivery.

Of course, this model somewhat oversimplifies: it assumes that outcomes are statistically independent, which in obstetrics is rarely the case (e.g., maternal age will affect practically every outcome parameter), and it primarily reflects nonidentical twin pregnancies, which obviously are the relevant ones when the number of embryos to be transferred in IVF is the subject of dispute.

That risks diverge if assessed per offspring versus per pregnancy is well recognized in reproductive medicine and is widely applied in genetic counseling of couples with multiple pregnancies before prenatal genetic diagnosis (25). Thus, why this knowledge has not been properly used in comparing risk/benefits of singletons and twins after fertility therapies is somewhat puzzling. Excluding the rare infertility patient who only wants one child, the uncorrected comparison of risk factors between singleton and twin pregnancies, as has been the practice in the literature, appears inappropriate.
Risk Comparisons

The medical literature is abundant in demonstrating increased maternal (26) and perinatal/neonatal (6, 7, 27–35) risks for twins in comparison with singleton pregnancies. However, most studies were based on spontaneous conceptions and not on pregnancies after infertility and/or IVF treatments. Van Wely et al. (36) summarized some of these data, based on recent European Society for Reproductive Medicine (ESHRE) data (37) and a national Danish data set (Table 1) (38–40).

Probably the most thorough analysis was presented by Helmerhorst et al. (28), who compared the outcome of singletons and twins with an exclusive concentration on assisted conception cycles. Reviewing 25 published studies on the subject (17 studies with and 8 without matched controls), these investigators concluded that singleton pregnancies after

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Adverse outcomes with twins delivered.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Spontaneous twins</td>
</tr>
<tr>
<td>Maternal</td>
<td></td>
</tr>
<tr>
<td>Sibai et al., 2000 (31)a</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.0 (1.6–2.6)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>2.6 (2.0–3.4)</td>
</tr>
<tr>
<td>MacKay et al., 2006 (26)</td>
<td></td>
</tr>
<tr>
<td>Maternal mortality</td>
<td>20.8 (vs 5.7; x 3.6)</td>
</tr>
<tr>
<td>Perinatal/neonatal</td>
<td></td>
</tr>
<tr>
<td>Fitzsimmons et al., 1998 (27)</td>
<td></td>
</tr>
<tr>
<td>Perinatal mortality/1000b</td>
<td>24</td>
</tr>
<tr>
<td>Helmerhorst et al., 2004 (28)a</td>
<td></td>
</tr>
<tr>
<td>Very preterm</td>
<td>—</td>
</tr>
<tr>
<td>Preterm</td>
<td>—</td>
</tr>
<tr>
<td>Very low birth weight</td>
<td>—</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>—</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>—</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>—</td>
</tr>
<tr>
<td>Neonatal ICU</td>
<td>—</td>
</tr>
<tr>
<td>Perinatal mortality/1000</td>
<td>—</td>
</tr>
<tr>
<td>Van Wely et al., 2006 (36)a</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>3.7 (3.3–4.3)</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>3.4 (1.2–9.4)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>2.0 (1.2–3.3)</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>3.4 (2.9–4.1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.7 (1.5–1.9)</td>
</tr>
<tr>
<td>Pinborg et al., 2004 (40)a</td>
<td></td>
</tr>
<tr>
<td>Birthweight &lt;2500 gram</td>
<td></td>
</tr>
<tr>
<td>Birthweight &lt;1500 gram</td>
<td></td>
</tr>
<tr>
<td>Gestational age 32–37 weeks</td>
<td></td>
</tr>
<tr>
<td>Gestational age &lt;32 weeks</td>
<td></td>
</tr>
<tr>
<td>Stillborn</td>
<td></td>
</tr>
<tr>
<td>Neonatal death within 7 days</td>
<td></td>
</tr>
<tr>
<td>Neonatal death within 1 year</td>
<td></td>
</tr>
<tr>
<td>Major birth defects</td>
<td></td>
</tr>
<tr>
<td>Minor birth defects</td>
<td></td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td></td>
</tr>
</tbody>
</table>

Note: If a twin pregnancy risk is, indeed, excessive, the relative risk (RR) of a twin pregnancy delivery has to exceed the RR of two singleton pregnancy deliveries combined (for further details, see text). This means that only a RR ≥ 2.1 denotes excessive twin pregnancy risk.

- Relative risk (RR) and 95% confidence interval (CI) in comparison with singleton pregnancies.
- Statistically significantly lower in IVF-conceived twins (P < .003).

assisted reproduction showed statistically significantly worse perinatal outcomes than spontaneously conceived singletons. In contrast, twin pregnancies after assisted reproduction demonstrated an approximately 40% lower perinatal mortality than spontaneously conceived twins (see Table 1). Fitzsimmons et al. (27) reported similar conclusions in the late 1990s.

As most published perinatal outcome comparisons between singleton and twin pregnancies are based on spontaneous conceptions, these observations have great importance. When applied to IVF, these data suggest that the outcome benefits of singletons, which are worse after IVF (28), have been greatly exaggerated and those of twins, which are better after IVF (28), have been minimized.

The Helmerhorst et al. (28) perinatal mortality data cannot necessarily be extrapolated to either perinatal morbidity or maternal outcomes, but these observations nevertheless suggest that data from spontaneous conceptions should be statistically corrected when applied to outcome assessments after assisted reproduction. As an intellectual exercise, Table 1 thus presents the outcome data corrected by 40%, fully recognizing that perinatal mortality data cannot necessarily be extrapolated to other adverse outcomes in offspring and mothers. Other outcome differences may be less divergent than perinatal mortality, but one can equally argue that some differences may be actually even greater. Such an argument is best supported by the observation that singleton IVF pregnancies demonstrate actually much worse outcomes than spontaneously conceived singleton pregnancies (28).

Lower maternal and neonatal risks should not be surprising because IVF patients usually are of higher socioeconomic status than women who spontaneously conceive (41). Their IVF twin pregnancies are diagnosed earlier and can be expected to receive earlier and overall better care. Moreover, younger women can be expected to have the larger percentage of monochorionic twins, representing a higher perinatal risk (25, 27). That this outcome benefit is not apparent in singleton pregnancies—and, indeed, turns into a disadvantage—is usually attributed to older age and underlying medical conditions in IVF mothers (28), though one very recent study suggested that outcomes of singleton IVF pregnancies also do not have to be inferior to spontaneously conceived singletons (42).

The most surprising finding of our literature review was, however, that not even one study has compared pregnancy outcomes corrected for the number of children born. Van Wely et al. (36) are the only ones to point out that most twin pregnancies result in the birth of two healthy children and that this fact deserves consideration. Not surprisingly, they conclude that twin pregnancies should not necessarily be considered adverse outcomes of assisted reproductive technologies.

As Table 1 demonstrates, outcome risks of twins have uniformly been overestimated: various twin pregnancy risks, except for minor exceptions, do not exceed relative risks of 2.0, representing the combined risk of two singleton pregnancies required to achieve the same outcome (two delivered children) as one twin delivery. Assessed in such a way, risks no longer demonstrate meaningful increases for twin pregnancies in either mothers or infants—and they often are lower than with two singleton deliveries. If we then further consider that IVF singleton pregnancies demonstrate higher adverse outcomes than spontaneously conceived singletons (28), the only remaining conclusion is that twin pregnancies (at least after IVF) do not represent higher overall outcome risks per newborn than singleton pregnancies.

This observation, of course, outright invalidates the principal argument in the literature of higher twinning outcome risks after assisted reproduction and thus also contradicts the information that is routinely provided to the public in support of single-embryo transfer.

The Cost Argument

Another frequently heard argument in favor of twin deliveries involves the allegedly higher costs for twin outcomes after infertility treatments (43–48). However, once again the literature uses incorrect statistical considerations. Analogous to the risk evaluations, cost also correctly should be calculated in reference to outcomes; that is, cost assessments that reference pregnancy rather than the delivered child do not make sense. They quite obviously should be calculated in reference to the ultimate outcome benefit—the number of newborn infants—yet not a single study has done so. This alone would most likely eliminate the claimed cost advantages of singleton pregnancies.

The published cost-effectiveness data suffer from an even larger statistical error: if true costs and benefits are to be compared between singleton and twin outcomes then both have to be considered per lifetime. Not a single published study has done that. Cost comparisons usually address infertility treatment costs (very short-term costs) (43, 47), perinatal and neonatal costs (short-term costs) (43, 44, 46–48), or limited follow-up medical costs (intermediate-term costs) (45); but they never address the long-term societal cost and benefits such as long-term medical costs and long-term earning power. Even in the absence of adequate studies, when the potential long-term earning power of a (second) human being is considered after twin delivery in the presence of a very low risk of lifelong handicaps (see Table 1), we conclude that twins offer considerable economic benefit to society over singleton deliveries. This argument is further enhanced in developed countries that are demonstrating negative population growth and are actively seeking ways to reverse low birth rates (48, 49).

Further Arguments in Favor of Twinning

The strongest argument in favor of twinning may be the infertile woman herself. Since the initial report on the topic in the mid-1990s (22), it has become well recognized that a high percentage infertility patients want twin pregnancies. Some studies have argued that patient desires may be affected by the degree of medical knowledge about risks associated
with twin pregnancies, but practically all studies on the subject have had to acknowledge varying degrees of desire for twinning in infertile patients (50–53). This is quite remarkable when we consider that the risk representations to patients have quite obviously been misleading and have biased patients against twin deliveries.

A desire for twins appears especially logical when associated with advanced female age and/or long-standing infertility (22). Thus, a minority of professional opinion has recently questioned whether twin pregnancies after IVF should be considered an adverse outcome (36, 54, 55). At the same time, the increased psychological and economic pressures from multiple deliveries (56) and the need to reconcile a couple’s position in regards to acceptable risk (57) have to be acknowledged.

A desire for twin delivery also appears logical when we consider that no infertile patient can be guaranteed that she will conceive successfully a second time. Infertility patients are highly educated and well aware of this fact, as documented by reports that they are willing to take very specific risks rather than face the chance of no pregnancy at all (53).

**CONCLUSIONS**

We have demonstrated that widely held opinions about excessive risks and costs from twin deliveries after infertility treatments are likely incorrect. In interpreting the published data, our conclusions are logical and appear statistically correct. Ideally, and as a more evidenced way of supporting this point, a prospective randomized study of patients undergoing one 2-ET versus two (or more) single-embryo transfers could be conducted to match patients for the same outcome (two children). Such a study would be at best difficult and most likely would be impossible to design.

How the very basic conceptual flaw we have discussed could enter the mainstream of professional thinking deserves some further exploration. For obstetricians, a comparison of maternal and neonatal outcomes after singleton and twin pregnancies does make sense; they mainly treat women after pregnancy has already been established, and they attempt to maximize outcomes by minimizing risks for each gestation. The paradigm used for spontaneous conceptions is based on post factum (after pregnancy has been established) interventions and, at approximately 99% of cases, it is based on singleton delivery (58). In infertile patients, circumstances are very different.

The conceptual error seems to have arisen from the assisted reproduction profession (perinatologists and reproductive endocrinologists alike) applying the obstetric paradigm to a completely different patient population. In the majority of cases, women who prospectively (and usually not spontaneously) attempt to conceive want more than one child and, depending on the fertility treatment, have the option (by some called risk) of choosing different probabilities of multiple births. This latter scenario clearly reflects different circumstances and requires a different treatment paradigm.

The situation we have described offers a warning beyond the limited confines of infertility therapy, applicable to medicine in general: treatment paradigms are population specific and cannot be automatically transferred. How costly such an error can be is demonstrated by this example: unwarranted attempts to reduce twin pregnancies after IVF have been shown to reduce overall pregnancy chances with IVF (19–21, 59). Nothing is as valuable to the infertile patient as the opportunity to conceive (53). The widely propagated practice of single-embryo transfer, which has been questioned in its ability to reduce twinning risk (60), should be discouraged unless patients have clear medical contraindications to twin pregnancies or only desire a single child for social reasons.

Inadvertent paradigm switches occur not infrequently in medicine. In infertility, another example has recently attracted attention, when preimplantation genetic screening of embryos for chromosomal abnormalities was reported to actually decrease rather than improve pregnancy chances with IVF (61).

Because IVF allows for relative control over twinning chance (16), these data also suggest that the procedure deserves further investigation as a potentially useful tool for safe, cost-effective improvement in population growth in countries with undesired low birth rates (49). In such countries, governments may find that subsidizing IVF may represent a cost-effective tool in their attempts at improving birth rates (49).

**REFERENCES**


