Re-Thinking Elective Single Embryo Transfer: Increased Risk of Monochorionic Twinning – A Systematic Review

Margaret Dziadosz^{a, b} Mark I. Evans^{c, d}

^aDivision of Maternal Fetal Medicine, Department of Obstetrics & Gynecology, St. Barnabas Medical Center Livingston, and ^bNew Jersey Perinatal Associates, Livingston, NJ, ^cMount Sinai School of Medicine, and ^dComprehensive Genetics, and Fetal Medicine Foundation America, New York, NY, USA

Keywords

Single embryo transfer · Monochorionic twins · Dichorionic twins · In vitro fertilization · Assisted reproductive therapy · Risk

Abstract

Background/Objectives: Multiple pregnancies have tripled in the United States over the past 3 decades. Attributed to increasing maternal age at delivery but more so assisted reproductive technological advances, an effort has been made to decrease twinning through elective single embryo transfer. We sought to review and evaluate risks of monochorionic twinning as a predictable consequence of increasing utilization of elective single embryo transfer on perinatal outcomes. Primary outcomes included twinning rates, fetal anomalies, growth, preterm birth, and mortality. Secondary outcomes included neurological and pulmonary disability, intrauterine growth restriction, and congenital cardiac anomalies and twin-twin transfusion syndrome. **Data sources:** PubMed and Embase. **Results:** A total of 106 studies identified by systematic search met the inclusion criteria. The trend for lower numbers of embryos transferred has inadvertently led to an increase in monochorionic twinning. This is associated with worse outcomes compared to dichorionic twinning and singleton gestations for all outcomes studied. **Discussion:** Of great concern for monochorionic twins is the

risk profile of significant morbidity and mortality. Transfer of 2 embryos should be considered to avoid higher risks inherent to the shared placental phenomena related to monochorionic twins.

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Background

Over the past 2 decades, infertility treatments, particularly IVF, have dramatically increased the success rate for infertile couples to have their own biological children. One common side effect, however, was a tremendous increase in multiple pregnancies which rose rapidly in the 1990s. For triplets and higher-order multiples, the peak incidence was around 2003. As better methods for control of ovulation medications, improvements in laboratory and clinical methods, and the realization of the increased risks of multiples evolved, the incidence has been steadily falling. Improved control of ovulation methods and extended culturing with blastocyst transfer have allowed for the reduction in the number of embryos transferred while maintaining satisfactory pregnancy success rates. However, blastocyst transfers have much higher rates of monozygotic twinning.

In the 1980s, it was commonly debated whether transfer of 4 or more embryos was appropriate in order to increase successful take home pregnancy rates. The debate

later fell to 3 embryos for transfer and then 2. Most recently, there is considerable pressure to make elective single embryo transfer (eSET) the standard of care. In jurisdictions where IVF is routinely covered by insurance or government programs, there is the luxury of taking multiple cycles to achieve a pregnancy. However, in locations where out of pocket costs can exceed USD 15,000–20,000 per cycle, there is great pressure to achieve a pregnancy in 1 cycle – thus historically increasing the number of embryos transferred per cycle.

Society for Assisted Reproductive Technology (SART) data show that in women under age 35 at delivery, the percentage of eSET increased from 4.5% in 2007, 9.6% in 2010 to 22.5% in 2013 [1]. The average number of embryos transferred has fallen from 2.2 to 2.0 to 1.8, respectively. As such, twinning from assisted reproductive therapies (ART) has decreased overall. When a single implanted embryo splits, the most common outcome is a monochorionic diamniotic (MCDA) twin pair. This type of twinning occurs in about 3% of ART cases and may be influenced by zona manipulation and extended cultures [2, 3]. Vital to note and counsel, however, MCDA twins have a vastly increased risk profile compared to dichorionic diamniotic (DCDA) twins. In addition, reducing MCDA twins is generally not done as this has a very high loss rate and residual neurological impairment rates are 6–10% in the surviving fetus [4]. As such, we present here a contrarian view and suggest that it may be preferable to continue to routinely transfer 2 embryos. This will increase the pregnancy rate but also the rate of DCDA twins and occasionally dichorionic-triamniotic triplets. If this option is chosen over eSET, then testing the health of both fetuses can be entertained. If desired, reduction to a singleton can be employed to further optimize maternal and neonatal outcomes [5].

Objective

The purpose of this review is to evaluate current risks of monochorionic twinning through a systematic review of the literature and to summarize the available evidence from existing clinical trials. These data may allow for guided management among caretakers to elect for or against eSET.

Data Sources

This systematic review was performed based on the Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA-IBD) recommendations [6]. All

data were obtained from previously published studies, and therefore Institutional Review Board approval was exempt.

Search Strategy

A systematic literature search was performed, with studies identified by searching PubMed and Embase (January 2005 to October 2016). To obtain additional, relevant data, we also searched the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Registry, and hand-examined reference lists from selected studies. Broad search terms were initially used to ensure that the most extensive range of publications was identified as follows: (maternal OR monozygotic twins) AND (fetal outcomes OR fetus outcomes OR pregnancy outcomes OR neonatal outcomes OR pregnancy complications OR maternal mortality OR maternal outcomes) AND (risks OR rates). After which, search terms were further limited to (maternal twins OR monozygotic twins) AND (fetal outcomes OR fetus outcomes OR neonatal outcomes) AND (risk OR risk factors) AND (IUGR OR preterm OR stillbirth OR anomaly OR anomalies OR mortality OR morbidity) AND (fraternal twins OR dizygotic twins) AND (fetal outcomes OR fetus outcomes OR neonatal outcomes) AND (risk OR risk factors) AND (IUGR OR preterm OR stillbirth OR anomaly OR anomalies OR mortality OR morbidity). Results were limited to English-language, peer-reviewed, and human studies.

Eligibility and Outcome Measures

Inclusion criteria required study of monochorionic twin gestations and reported outcomes compared to that of singleton gestations or dichorionic twin gestations. Types of comparative data collected included epidemiological data, cost analysis, and fetal and maternal morbidity and mortality data. Our primary outcomes evaluated included twinning rates, fetal anomalies, growth, preterm birth, and mortality. Predefined secondary outcomes included neurological disability, pulmonary disability, intrauterine growth restriction (IUGR), and congenital cardiac anomalies and twin-twin transfusion syndrome (TTTS).

Study Selection

Manuscript titles and abstracts identified by the literature search were screened. The material and methods of each article that was deemed relevant were reviewed to determine eligibility. The complete manuscript was then reviewed to confirm eligibility.

Fig. 1. PRISMA flow diagram. This figure illustrates the systematic search of included and excluded articles.

Data Extraction

For each included article, we extracted the type of gestation and relevant outcome information pertaining to predetermined outcome data. Large studies were interrogated for potential overlap. Our primary goal was to evaluate the most current risks of monochorionic twinning compared to dichorionic twinning and singleton gestations. The Meta-analysis of Observational Studies in Epidemiology guidelines were followed for this systematic review [7].

Results

The systematic search produced 3,941 results. After more defined, secondary terms were applied, 850 publications remained. Titles and abstracts of these records were screened, resulting in the exclusion of an additional 484 records (282 were not relevant and 202 overlapped between databases). Of 366 relevant articles, 284 were excluded due to insufficient outcome data or non-peer-reviewed sources of origin. An additional 24 articles of importance, published between 1978 and 2004, were retrieved by hand searching reference lists of 82 relevant articles. A total of 106 articles met final inclusion criteria for systematic review (Fig. 1). Twenty-two relevant articles informed epidemiological data, 22 provided data about fetal anomalies, 13 yielded relevant information about fetal growth, 8 about preterm birth, 25 informed specific effects of single placentation, 19 informed neurological disability, 3 informed pulmonary disability, and 20 pertained to neonatal mortality, with some overlap between groups.

Epidemiology

The twinning rate, or births in twin deliveries per 1,000 total births, tripled from 1980 through 2009 to 33.2 per 1,000 births [8–16]. After stabilizing for several years, it again rose by 2% in 2013 to 33.7 per 1,000 births [17, 18]. The twinning rate increased most among non-Hispanic blacks and Hispanic women but has remained stable among non-Hispanic whites. The most recent data reveal that 132,324 neonates were born as twins in 2013. Of these, 11.3% were born at <32 completed weeks, and 56% were born at <37 completed weeks [18].

Naturally conceived monozygotic twinning remains constant at 3–5 per 1,000 births; two-thirds of naturally occurring monozygotic twins are MCDA, but they represent only about 20% of total twins because of the tripling of total twin births from infertility treatments. Rising rates of multifetal gestations are associated with ART and also with increasing maternal age at delivery [19–23]. The multiple birth rate increased to 71 per 1,000 live births for maternal age over 40 at conception compared to 16.3 per 1,000 at age 20. Elderly gravidas experience more obstetric complications including hypertensive disorders or pregnancy, diabetes, abruption, and labor abnormalities. These maternal morbidities are compounded by maternal complications inherent to a multiple gestation including hyperemesis, diabetes, hypertensive disorders, anemia, hemorrhage, and cesarean delivery [24–26].

Twin gestations are significantly more costly than singleton pregnancies, incurring a 10 times greater cost in the first year of life from prematurity and associated complications [27, 28]. This is mostly because infants born of twin gestations have a higher frequency of fetal and neonatal morbidity and mortality compared to singletons,

which is most closely associated with preterm birth. In 2013, according to the National Vital Statistics Report, 1 of every 2 twins were born either preterm or had a low birth weight (<2,500 g) and 9.75% were born with a weight of <1,500 g [29].

Among twins, MCDA gestations pose greater risk than DCDA pregnancies. They pose a disproportionate disease burden on the fetuses and live-born neonates as a result of a single, shared placenta.

Anomalies

Overall, multifetal gestations have a greater risk of congenital anomalies than singletons.

Dichorionic

For Mendelian disorders, there are 2 chances per each pregnancy. So, for 1 of 2 dizygotic twins the risk of at least 1 being affected is: $3/4$ that the first one is not affected $\times$ $3/4$ that the second one is not affected, or $9/16$ that neither are affected and thus $7/16$ (44%) that at least 1 is affected. For chromosomal abnormalities, the maternal age-related risk of having 1 of 2 fetuses affected compared to maternal age-related singleton gestations is almost double. Therefore, a woman carrying dichorionic twins at the age of 30 has the risk portfolio for carrying an aneuploid affected child equal to that of a 35-year-old mother carrying a singleton [30].

Monochorionic

For Mendelian and chromosomal anomalies, whatever one is, so is the other, so the overall incidence is equal to singletons in MCDA twins. However, although MCDA twins are of presumed identical genetic makeup, they are more likely to be phenotypically discordant for major structural anomalies with the risk of major structural anomalies being 6–8%. This is much higher than for both DCDA twins (1–2%) or singleton gestations [31, 32].

The risk of structural anomalies alone in MCDZ is slightly higher than twice that of singletons. The etiology of this is more than simply because of the added probabilities of more than 1 fetus to consider. There is a higher prevalence of midline and lateral defects including cloacal extrophy, anal atresia, anencephaly, spine defects, and cardiac defects in MCDA twins. This may be explained by the more difficult segmentation, where major body axes rearrange, in a MCDA gestation, as well as early hypoxia and damage to the early embryo that divides [33, 34]. In addition, local epigenetic factors may influence gene expression differently between the MCDA pair [35].

MCDA gestations face more complications due to the high likelihood of unbalanced volume distribution of placental vascular supply leading to TTTS, twin anemia polycythemia sequence (TAPS), and selective fetal growth restriction. Because of vascular connections in a single placenta causing unbalanced transfusion, an anomaly in a single twin may negatively affect a healthy co-twin. The pathology can be either due to compounding hemodynamic instability or with eventual death of the co-twin that occurs in 10–25% of cases. Cerebral damage occurs in a quarter of the surviving twins upon death of a co-twin due to exsanguination into the circulation of the demised twin and detrimental deoxygenation of the survival causing permanent damage [13, 36, 37].

MCDA gestations also appear to be at increased risk of congenital cardiac anomalies. Though the etiology is not completely understood, it is attributed to both teratogenic-hemodynamic instability and morphogenic anomalous embryological development with early division of the fertilized ovum [38–40]. The risk of congenital heart disease (CHD) is increased by approximately 60% in twins compared to singletons [41–43]. A large survey from northern England between 1998 and 2010 revealed that MCDA twins are at 82% increased risk for CHD than DCDA twins and a 292% increased risk compared to singletons with a prevalence rate of 202.8 per 10,000 total births [44]. MCDA gestations are also specifically at increased risk for more severe CHD such as single ventricle, hypoplastic left heart, and hypoplastic right heart as well as mild CHD such as atrial and ventricular septal defect (most common anomaly), pulmonary valve stenosis, and patent ductus arteriosus that persists beyond 37 weeks of pregnancy [34, 44]. At least 5% of MCDA gestations will have at least a single affected fetus detected, while upwards of 9% will be affected in cases of TTTS, 15–23 fold higher than the general population [33, 41]. Therefore, every MCDA pair should be evaluated with fetal echocardiography [15, 16]. Many of the more severe congenital cardiac anomalies have a high likelihood of intrauterine fetal death, which is especially detrimental to the unaffected twin in an MCDA gestation.

Death of a co-twin increases the risk of long-term cognitive and neuromotor disabilities in MCDA, but not DCDA twins. MCDA survivors have a significant rate of neurological morbidity, reported to be as high as 10–30% [45, 46]. DCDA twins have lower Mental Processing Composite Scale scores at 5 years of age compared to matched dichorionic twins [47]. Therefore, selective feticide may be more specifically indicated as an intervention for the unaffected twin in such cases [48].

Growth

Growth discordance is defined as a difference of at least 20% between fetuses. Gestations with discordant growth, but in which both twins still in the normal range are likely not at significantly increased risk of mortality. However, when there is growth discordance and at least 1 fetus is growth restricted, there is nearly an 8-fold increased risk of major neonatal morbidity [49–54]. Growth-restricted twins also have a greater rate of both morbidity and mortality when compared to age-related growth-restricted singletons [55].

Selective IUGR is associated with both fetal mortality and poor neurological outcomes. It occurs due to disproportionate placental sharing due to abnormal vascular connections. It may be diagnosed either of 2 ways: both a fetal weight of less than the 10th percentile with or without significant growth discordance or simply a growth discordance greater than 25% between twins [8–10, 25, 56].

Monochorionic

Selective IUGR in MCDA twins is associated with increased risk of demise of the smaller twin and neurological damage in the larger twin. The incidence of neurological damage occurring in the larger twin persists even when the smaller co-twin survives [25].

Preterm Birth

Twin pregnancies are 6 times more likely to deliver preterm and 13 times more likely to delivery prior to 32 weeks' gestation.

Monochorionic

MCDA gestations have an 87% likelihood of delivering preterm, which is significantly more common than both DCDA and singleton gestations. They are more significantly likely to deliver prior to 28 weeks, 34 weeks, and more likely to experience NICU admission and intrauterine fetal demise [57, 58]. Often, this is due to other inherent morbidities experienced by MCDA twins, such as IUGR and preeclampsia [59]. Simoes et al. [60] studied fetal outcomes of twin gestations based on chorionicity only in ART mothers and found that MCDA twins conceived by ART were significantly more likely to be delivered preterm and to have lower birth weights. The higher prematurity rates also led to an increased early neonatal death rate in MCDA twins.

Although it is agreed upon that the optimal timing of delivery is earlier for twins than singletons, controversy remains regarding optimal delivery time balancing the

risks of prematurity and mortality, with several large studies promoting delivery between 37–38 weeks' gestation [61, 62]. In addition to medically indicated or spontaneous labor causing preterm birth in MCDA twins, literature supports iatrogenic preterm delivery of MCDA twins. The American College of Obstetricians and Gynecologists recommends delivery of MCDA gestations between 34 0/7 and 37 6/7 weeks [63]. The benefit of promoting late preterm delivery has been studied and confirmed due to a decreased risk of perinatal and neonatal mortality in such cases, which rises with prolonged gestation [64].

Morbidity

The Single Placenta

Monochorionic. MCDA gestations develop TTTS in 8–15% of gestations. In dichorionic-triamniotic triplets, the TTTS rate is over 50% [65]. TTTS accounts for nearly 50% of the deaths in MCDA gestations [66, 67]. TTTS complicating MCDA gestations is associated with poorer long-term outcomes including a 22–26% incidence of neurological impairment. Those who undergo laser coagulation have better outcomes, but still have an incidence of neurological impairment upwards of 17%. Development of CP specifically, occurred in 21% of those with TTTS and 7% of those with TTTS who underwent laser treatment [49, 68, 69]. TTTS is associated with these risks independent of death of a co-twin. Treatments including laser ablation can yield significantly morbid outcomes to the pregnancy. No data conclusively demonstrate that any intrauterine therapy including amnioreduction or laser ablation improves neurocognitive or neuromotor outcomes [70]. TTTS also lends consequences to the cardiovascular status of the fetuses with progressive decompensation as disease status progresses. The recipient twin develops cardiomyopathy and abnormal diastolic and systolic function [70–73]. Interestingly, MCDA twins conceived after eSET splitting may experience less TTTS [74]. This suggests a potential different embryological process inherent to ART-conceived monozygotic twinning.

The TAPS is another chronic disease sequence affecting MCDA pairs. It involves unbalanced blood distribution between twins leading to anemia in the donor twin and polycythemia in the recipient twin. This condition occurs in approximately 5% of MCDA pregnancies spontaneously. It is seen even more frequently (12%) after fetoscopic laser treatment for TTTS [75–80]. Poor neurodevelopmental outcomes including isolated cognitive delay, motor delay and cerebral palsy rates range greatly be-

tween 2 and 20% in both the donor and recipient twins who are affected by TAPS [81].

Cognitive development is impaired in twins compared to singletons according to the Bayley Scales of Infant Development Index [82, 83] in preterm infants. There is consistent cognitive disadvantage among twins seen in population-based studies [84]. Fifteen percent of MCDA pairs affected by TTTS, growth discordance, or death of a co-twin will have an IQ that is >2 standard deviations below the mean compared to 3% of DCDA twins [85]. An exception to this includes a Danish cohort of ninth graders which did not consider children disabled and not available for study in the normal school system [79, 86].

Autism spectrum disorders are reported to be 10- to 14-fold higher in MCDA twins and 4.5-fold higher in dizygotic twins compared to singletons [87, 88]. This is likely compounded by lower birth weight in twins, lower gestational age at birth compared to singletons, as well as increased parental age, all of which are associated with not only autism spectrum disorders, but also twin pregnancies.

Neurological

Neurodevelopmental disability is higher in multiple gestations compared to singletons invariably due to lower birth weights and earlier gestational age at delivery. Singletons tend to have higher IQ by 1.4–5.1 points in a cohort of full-term, normally grown neonates at birth [84]. Though there is no apparent effect of chorionicity on IQ among twin pairs, a difference in IQ has been found among children born from multifetal gestations compared to singletons [89, 90]. Twins born <32 weeks' are 2 times more likely to develop intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) compared to singletons born of the same preterm gestational age [91]. Wadhaman et al. [82, 83, 92] reported a large cohort of infants born <1,000 g with a higher rate of CP in twins (8.4%) over singletons (6.3%) at 18–22 months of age. For infants born <36 weeks', the relative risk of at least 1 twin developing PVL is 2.181 ($p < 0.001$) compared to singletons. PVL was diagnosed in the first twin 50% of the time and in both twins 12% of the time. Monochorionicity was relevant for 27% of affected twins, thereby indicating a high incidence in DCDA twin pairs as well [69].

Overall, outcomes in multiples are worse than in singletons even after comparing for these covariates. Multifetal gestations pose an increased risk of developing cerebral palsy. The rate of cerebral palsy is 7% among twins compared to 1.6% among singletons [93, 94]. Though the mechanism is undoubtedly complex, the injury causative of development of cerebral palsy in twin gestations is an-

tenatal in over 80% of cases [95–97]. Surprisingly, there is no significant difference between DCDA twins and singletons when controlling for complications of prematurity [98]. Therefore, the difference between twins and singletons may be largely due to MCDA twins.

Monochorionic. Monochorionic gestations are at greater risk of neurological sequelae due to placental vascular anastomoses which allow for hemodynamic imbalances such as hypovolemic shock or cerebral ischemia from hypoperfusion [98]. In a study that looked at infants born <32 weeks', MCDA twins were 6 times more likely to develop cerebral palsy compared to DCDA twins after adjusting for gestational age, gender, cesarean delivery, neonatal bacteremia, and preterm rupture of membranes. This is consistent with the notion that MCDA gestations are at a greater risk due to placental and hemodynamic imbalances compared to DCDA that are more comparable to singleton gestations.

There is a higher rate among MCDA twins compared to DCDA twins [95, 99–101]. The type of cerebral palsy is also different in twins. In comparison to singletons, multiples have higher rates of spastic (91 vs. 87%) and bilateral (73 vs. 65%) cerebral palsy. These types are most likely to be associated with white matter injury, namely PVL and also basal ganglia lesions [93].

Twins at term and of normal weight have higher rates of cerebral palsy than singletons. The overall relative risk for cerebral palsy in twins born $\geq 2,500$ g is 3.3–5.5 compared with singleton [102]. Some data findings are inconsistent. A prospective, non-population-based study showed better long-term outcomes at 2 years than expected. The majority of twins had normal development at 2 years. Cerebral palsy was associated with TTTS, death of a co-twin or cystic PVL development, though there was no significant difference between DCDA and MCDA twins otherwise [98]. Another study by Livinec et al. [103] revealed no difference in cerebral palsy rates between MCDA and DCDA twins when covariates including gestational age at delivery, gender, in utero demise of a co-twin, pregnancy complications and receipt of steroids were controlled for. Inconsistency of data is likely attributable to small study numbers, inappropriate consideration of covariates, and overly early age at evaluation for diagnosis of cerebral palsy in many studies.

Pulmonary

Fifty-seven percent of MCDA twins experienced respiratory distress after birth [59]. A significantly higher number of twins develop respiratory distress syndrome, bronchopulmonary dysplasia, and pneumothorax [104].

Three percent of MCDA twins affected by TTTS are at risk of development of persistent pulmonary hypertension, compared to 0% in those unaffected by TTTS [105].

Mortality

Twins are more likely to not survive the first year of life compared to singletons [18]. The infant mortality among twins reaches 24% compared to 5.4% in singletons [31, 45, 66, 67, 71–73, 106, 107]. Multifetal gestations are at an increased rate of fetal and infant mortality. 5% of twin gestations experience death of at least 1 fetus in the second or third trimester. There is a 5-fold increased risk of stillbirth among twin gestations. MCDA twins have a higher rate of stillbirth than do DCDA twins [108]. Monoamniotic twins have the highest rate of stillbirth, with rates quoted as high as 80%, primarily due to cord accidents due to entanglement in utero. In the event of a rare condition called twin reversed arterial perfusion, or TRAP, where the pump twin perfuses not only itself, but also a nonliving twin via a high-flow, low-resistance circuit, mortality of the pump twin reaches 50% due to a high likelihood of cardiac failure and hydrops fetalis. After the death of a single fetus in a twin pregnancy, there is a 3% risk of demise in the co-twin of a dichorionic gestation and 15% in a MCDA gestation.

In the event that a co-twin survives in a MCDA pair after a single demise, there is significant risk of neurological sequelae in the surviving twin upwards of 18% [109–113]. Unfortunately, immediate delivery of the surviving twin does not eradicate this risk [114]. There is also risk of neurological abnormality if this occurs in a DCDA pair, though much lower at approximately 1%. There is a 7-fold increased risk of neonatal death, primarily due to preterm birth among twins [94, 115, 116].

Discussion

The aggressive approach of both ovulation induction methods and IVF embryo transfers has led to an unacceptable incidence of multifetal pregnancies in the past decade. These numbers have been dramatically reduced over the past several years – diminishing one problem but replacing it with another [117, 118]. There are other important considerations to ART as well. Day 3 embryos, with higher-order numbers of cells compared to fresh or day 2 samples, have a higher success rate in ART. It would seem that healthy day 3 embryos that have not undergone freezing or other manipulations causing trauma may lead to fewer anomalies and lower costs.

However, data show that there is no difference in outcome when considering day 3 versus day 5/6 embryo transfers. In fact, frozen-thawed embryo transfers fare better than fresh embryos. In twins, neonatal outcomes including birthweight, small-for-gestational age, and prematurity rates were comparable in the vitrified and the fresh group. Furthermore, the rate of major congenital malformations in live-born neonates is comparable between the vitrified group and the fresh group in twins (2.4 vs. 2.7%; AOR: 0.51; 95% CI: 0.05–5.72) [119–122].

Embryo quality may vary considerably between laboratories. ART volume, staffing experience, equipment, air quality and organizational issues are just a few of the factors that influence IVF center quality and success rates [123–125]. Grading systems are applied to assess quality based on cell number, cell regularity, fragmentation, and general appearance; this is subjective and allows for significant variation.

Blastocyst transfers have dramatically increased the implantation rate of embryos such that the eSET numbers have risen dramatically. However, there is inherent teratogenicity with extended culturing which leads to both increased monozygotic twinning and increased anomalies – much of it defects of laterality. With loss rates of 10–20% and neurological impairment rates of 6–12%, with MCDA twins, fetal reduction is not a realistic possibility in the vast majority of instances. Thus, it is “take it or leave it.” Neither is a desirable outcome.

If one has 2 embryos, and the choice is to transfer 2 in 1 cycle, or 1 each in 2 cycles, data have shown that the overall pregnancy rate is actually higher with 2 in 1 cycle [126–128]. There is the potential for DCDA twins and rarely dichorionic-triamniotic triplets. In these circumstances, we have shown that in experienced hands, genetic diagnosis of multiples by chorionic villus sampling (CVS) with fetal reduction produces outcomes comparable to having a singleton in the first place [129–132].

Because a genetic evaluation is done, the residual risks of chromosomal and structural anomalies are actually lower than for the typical singleton pregnancy. With the availability of array comparative genomic hybridization, evaluation on CVS obtained villi prior to reduction if chosen by the patient, an even further detailed evaluation can be done to reduce morbidity and mortality [133]. This has to be compared with the delay in obtaining the final diagnosis, which is a downside for patients considering reduction. With the understanding that reduction may not be an option for many individuals due to personal reasons, our experience shows that CVS and reduction are safe, effective, and significantly improve out-

comes in appropriate cases [5, 129]. There is extensive literature, as cited in this review, which supports that conclusion. In fact, pediatric data have suggested that the outcome of delivering babies in pregnancies after fetal reduction may be better than the same number without fetal reduction. This may be due to practitioner selection of healthier gestations by a variety of methods, thereby decreasing the residual risk of neonatal abnormalities. It should be observed that there is bias in personal practitioner experience. Risks of fetal reduction procedures likely vary among providers. Data are limited, though experience from amniocentesis, chorionic villous sampling, periumbilical blood sampling and female pelvic surgeries do indicate that high-procedure volume is related to better patient outcomes [134].

On balance, we believe that patients undergoing ART would be best served if they were presented not only the option of eSET but also of transferring 2 embryos. With development of MCDA twins, it is vital that patients understand the inherent risks of this type of twinning. With the transfer of 2 embryos, the singleton pregnancy rate is higher, and if there are DCDA twins or MCDA triplets, there is the possibility of genetic diagnosis and reduction, which clearly improves outcomes.

Disclosure Statement

Authors disclose any sponsorship or funding arrangements relating to their review and all authors disclose any possible conflicts of interest.

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