

# Redefining Success in IVF: Reducing the Burden of Care

Highlights of an Expert Roundtable Meeting on Single Embryo Transfer in IVF



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A Message from Our Chair	p.4
Primum Non Nocere: IVF - Where Are We Now?	p.6
Redefining IVF: Technical Advancements, Personal Insights	p.10
The Pathway To Single Embryo Transfer (SET): Stakeholder Perspectives	p.16
The Pathway Forward: Implementation Recommendations for SET	p.24
References	p.27



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# A Message from Our Chair

As the great scientist Albert Einstein noted, “We can’t solve problems by using the same kind of thinking we used when we created them...To raise new questions, new possibilities, to regard old problems from a new angle, requires creative imagination and marks real advance in science.”

Assisted reproductive technologies (ART) and in vitro fertilization (IVF) have been marked by the contributions of pioneering researchers – Howard Jones, Georgeanna Jones, Gregory Pincus, Robert Edwards, Patrick Steptoe and others - who had the courage, foresight and ability to think beyond the status quo, to ask important questions and to inspire ongoing research in efforts to improve outcomes and quality of care for hopeful parents everywhere.

Today, we are seeing remarkable advances in our understanding of reproductive physiology, embryonic development, and the IVF process, as well as the development of powerful and validated new genomic and culture-related tools that are ushering in an era in which clinical outcomes can improve dramatically and redefine what success means.

**IVF touches many stakeholders – patients, their offspring, healthcare providers, insurance companies, as well as employers of patients** undergoing the time-consuming and invasive treatments. Each of these groups may primarily focus only on its own immediate concerns and needs, not incorporating how each step and choice along the path are intricately tied to one another. Therefore goals for safe and effective IVF treatment must be multi-dimensional in order to address the near and long-term issues faced by each group of stakeholders:

- **Increase pregnancy and delivery rates**
- **Decrease miscarriage rates**
- **Eliminate multiple gestations especially higher order ones (except for the rare monozygotic twins)**
- **Decrease time in treatment and number of cycles required to attain a delivery**
- **Greatly reduce downstream obstetric and pediatric consequences of infertility care and improve the health of mothers and infants**
- **Improve cost-effectiveness of healthcare expenditures**

A recent national review found that fewer than 19% of embryos that were considered to be of sufficient quality to be transferred, actually implanted and progressed to delivery. Despite ongoing improvements in the spectrum of IVF procedures and technologies, success rates in the United States, as measured by live birth rates, have plateaued at approximately 40%, and double embryo transfer (DET) has continued to predominate in order to maximize live birth rates.

Unfortunately, this strategy means that the incidence of twins deriving from infertility treatments is approximately 20 times greater than that of spontaneously conceived twins.

“I would love for single embryo transfer to be the standard of care. I would hope that all patients have access to the kind of care that would include genomics and other validated services and really allow people who want to have kids to have them safely one at a time.” *Dr. Richard T. Scott, Jr.*

Although twins are considered one of the single most important adverse outcomes of IVF cycles that result in a viable pregnancy, one of the ongoing impediments to adopting single embryo transfer (SET) as the standard of care has been that DET reliably resulted in higher delivery rates per single fresh cycle than SET. Today, however, synchronous transfer of a single euploid embryo provides delivery rates of 55% to 65% through maternal ages of 42, exceeding national delivery rates.


These outcomes are broadly achievable now by integrating our knowledge of the entire IVF process with advanced technologies. Through these synergies, a new paradigm has emerged and it is now possible to:

- Consistently perform extended embryo culture to the blastocyst stage
- Improve safety of embryo biopsy through trophectoderm biopsy
- Enhance embryo selection process through embryonic aneuploidy screening
- Ensure synchrony between blastocyst maturation and endometrial receptivity to implantation
- Utilize dramatic improvements in cryopreservation to allow for synchronous transfer

On February 22, 2013, a multi-disciplinary panel of experts convened to review the implications and downstream impact of current standards of care in IVF; the current status of SET for IVF; the benefits of new technologies and procedures; and the potential of SET as the standard of care going forward.

Hosted by Reproductive Medicine Associates of New Jersey (RMANJ), the meeting included representatives of key stakeholders in the field of infertility who provided their unique perspectives on the challenges and opportunities afforded by ongoing advances in IVF. This report summarizes highlights of their insights and recommendations, focusing on the ripple effects associated with one important decision: **establishing SET coupled with embryonic screening as the optimal path to one healthy baby at a time.**

The time is now to redefine what success in IVF means, not only for healthcare providers who manage the unintended burdens of multiple gestations and deliveries from IVF treatment but for hopeful parents everywhere.




Richard T. Scott, Jr.  
MD, FACOG, ALD/HCLD



A microscopic view of a cell, likely a zygote or early embryo, showing a nucleus and surrounding cytoplasm. The image is colorized with a blue and green palette. A solid blue horizontal band is overlaid across the middle of the image, containing the title and subtitle text.

# Primum Non Nocere

*IVF - Where Are We Now?*



More than 30 years after the first successful in vitro fertilization (IVF) procedure, the American Society for Reproductive Medicine (ASRM) stated their opinion that “The goal of infertility treatment is for each patient to have one healthy child at a time.”<sup>1</sup> Nevertheless, twin birth rates in the United States continue to rise. Although the majority of twin births are naturally conceived, the incidence of twins resulting from stimulated ovulation and assisted reproductive technologies (ART) is more than 20 times greater than that of naturally conceived twins.<sup>1</sup>

The incidence of twins resulting from stimulated ovulation and assisted reproductive technologies (ART) is more than 20 times greater than that of naturally conceived twins.<sup>1</sup>

It is well-recognized that, in general, multiple gestations and births increase pregnancy-related complication rates, long-term negative health consequences, and overall costs in comparison with singleton gestations and births.<sup>2,3</sup> These facts have important implications for IVF policies and practices because IVF twins are a potentially avoidable treatment complication.<sup>4</sup>

Good medical practice would suggest that where the means exist to improve outcomes (including risk amelioration), then the relevant knowledge and technology should be applied in keeping with the principle of “First, do no harm.” As IVF science and technology continue to advance rapidly, an ongoing challenge will be to define what constitutes an increased risk outcome and from whose perspective.

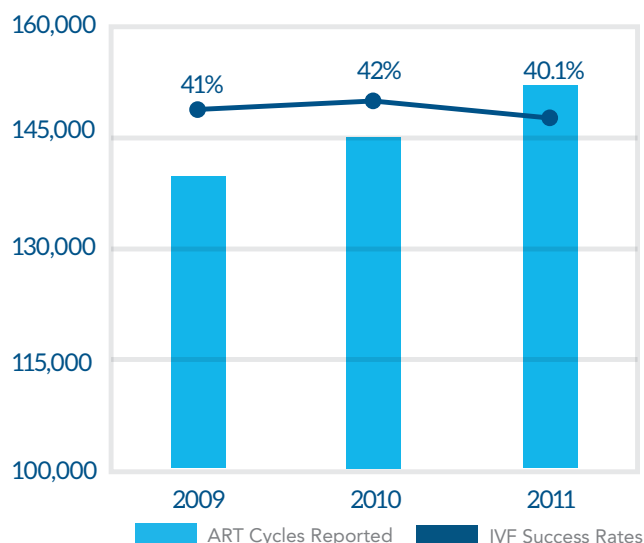
“The complications that occur from IVF, which to some extent have been inevitable in the past, may be behind us now.” *Dr. Richard T. Scott, Jr.*

## IVF - Where We Are Now?

Since the birth of Elizabeth Carr, the first US IVF birth in 1981, there have been major advancements in ART and IVF which have had a profound impact on care of the infertile couple and their chance for success. Today, across the approximately 482 IVF programs operating in the US<sup>5</sup>, you will find that most programs are following similar clinical, embryologic, and patient care standards.

However, recent advancements in the areas of extended embryo culture, embryo biopsy, preimplantation genetic diagnosis, and endometrial synchrony are leading to improved safety and outcomes for hopeful parents everywhere. At a time when US IVF delivery rates are hovering around 40%<sup>5</sup>, implementation of new protocols and well-validated technologies are leading to delivery rates well above 60% per cycle for women under 35.

Figure 1. ART cycles and live birth rates



“One of the issues is the perception that multiples are very desirable, but there are also many, many problems associated with multiple pregnancies.” *Dr. Gloria A. Bachmann*

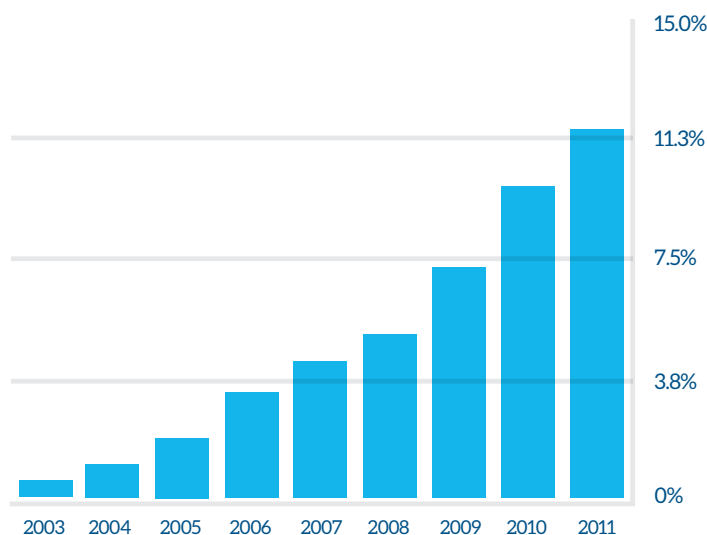
There has been virtually no change in national success rates in the period between 2009 through 2011. In its 2011 report, the Society for Assisted Reproductive Technologies (SART) reported on 154,412 cycles (Figure 1).<sup>5</sup> The percentage of cycles resulting in live births for women under the age of 35 years, considered a good prognosis group, remained at about 40%. (Figure 1).<sup>5</sup>

In women less than 35 years of age, only 11.7% of cycles were elective SET (eSET). Although the rate of eSET among younger women has increased steadily since 2003 (Figure 2)<sup>5</sup>, the data suggest clearly that SET has not begun to be accepted as the standard of care, and key challenges remain.

Based on surveillance data from 2009, 43.7% of infants conceived by ART procedures were twins. In contrast, twin births comprised only 3.3% of total US births in the same year.<sup>6</sup>

Further, SART recorded more than 23,000 twin deliveries from fresh/non-frozen embryos in 2011 across all age groups, with the vast majority occurring in those less than 35 years old. (Table 1)<sup>5</sup> The average number of embryo transfers was 2.5 across all age groups. In women less than 35 years old, the percentage of twin live births was 30.8%. (Table 1)<sup>5</sup>

Figure 2. Rate of eSET among women less than 35-years of age



“The risks of twinning are underestimated by the general public. Often people think it’s something special to be celebrated, but it’s not always the case.” *Dr. William Henry Barth, Jr.*



Table 1. SART 2011: Clinic summary report on fresh embryos from non-donor oocytes<sup>5</sup>

Age Group	<35	35 - 37	38 - 40	42	>42
Number of Cycles	39,721	19,930	20,130	10,277	6,033
Average Number of Embryos Transferred	1.9	2.1	2.5	3.0	3.1
Percentage of Cycles with eSET	11.7%	6.5%	1.9%	0.6%	0.5%
Percentage of Live Births with Twins	30.8%	26.7%	21.1%	14.9%	10.6%

### Balancing Risks and Benefits: Perceptions and Reality

The panel discussed at length both the needs and challenges in reframing the discussion with patients about the risks and benefits of multiples in ART cycles. The panel agreed that establishing SET as the standard of care with patients and infertility specialists alike requires no compromise of success rates when the key elements of the new paradigm - embryonic screening, trophectoderm biopsy, and endometrial synchrony are applied.

A key barrier to the acceptance of SET has been that DET has consistently resulted in higher delivery rates per fresh cycle than SET. These data, however, reflect the scenario in which effective screening techniques are not used.<sup>7,8</sup> For example, the live birth rate (LBR) was approximately 2-fold higher for DET than for SET as shown in a systematic review and meta-analysis, even though the risk of multiple gestations was reduced significantly.<sup>8</sup>

Although the addition of a second cycle with a single frozen embryo transfer can equalize cumulative LBR, the **perceived risk** of failure has had greater salience to patients. **Actual risks** associated with twin or higher order births are usually not considered by patients. The stresses, financial burdens, and lack of knowledge about adverse outcomes of multiple births likely contribute to patient preferences for DET.

Until now, technological advances have not provided consistent methods to increase the probability of success with SET, thereby helping to reinforce and maintain the status quo of DET as the generally practiced standard of care. The technology, however, is now available to change the odds. Perceptions of the benefits and harms remain another issue.

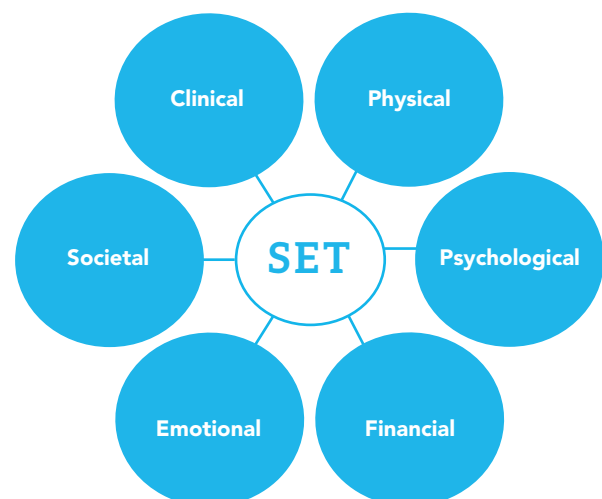
### The Costs of Twin Births: Overview

A number of studies have provided data on costs of multiple births harms and increased costs of multiple IVF births, including maternal and perinatal morbidity and mortality.<sup>9</sup> Studies comparing outcomes from DET and SET have been criticized for not including 2 singleton pregnancies. A recent study, however, overcame this limitation by comparing neonatal outcomes from IVF twin pregnancies after DET with 2 IVF singleton pregnancies.<sup>10</sup> In that study, both neonatal and maternal outcomes were characterized as “dramatically” worse for IVF twin pregnancies. The health consequences for parents and IVF twins are just one aspect, albeit multi-faceted, of the burden of multiple pregnancies.

All of the meeting participants agreed that the health care consequences are inextricably linked to substantial economic costs, and that all are likely to be underestimated in current studies. Lee Collins from RESOLVE commented on the impact of SET on both mother and child, “As long as success rates are similar, it’s important for patients to consider single embryo transfer because the studies all show that a single baby is healthier. It’s healthier for the mother and it’s healthier for the child.”

Dr. Barth added, “In my specialty in maternal fetal medicine, I see the downside of it more frequently than another might. **The biggest risk with twinning is preterm birth, and preterm birth remains the number one cause of newborn morbidity, mortality and suffering.** It eclipses every other problem. It eclipses everything. If there’s an intervention that makes sense, that reduces the risk of prematurity, that’s a huge thing for us.”

The panel agreed that for many patients and providers there are many unintended and unnecessary costs and burdens across a number of areas that can be reduced by SET as illustrated below.





# Redefining IVF:

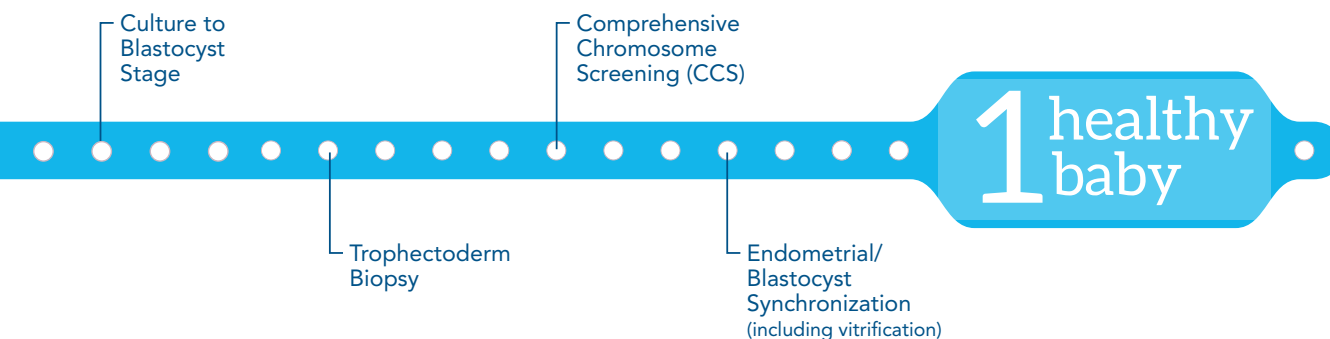
*Technical Advances, Personal Insights*



Today, the IVF experience continues to evolve. Although limited gains in safety and success rates characterize the recent past, several years of research now provide class 1 data that promise to redefine the current paradigm. New technological advances, like comprehensive chromosome screening (CCS) in concert with increased understanding of reproductive physiology, are now in a position to supplant the current clinical paradigm in which embryonic morphology is the primary driver of embryo selection for IVF transfer. These new technologies can provide uncompromised delivery rates with fewer treatment cycles through synchronous transfer of a single euploid embryo.

#### Advancements Making Single Embryo Transfer Successful

When used in conjunction, the latest procedures and screening technologies help pave the way to delivering 1 healthy baby.



“For older women, screening is a way to find the needle in the haystack. Even when you’ve got a lot of embryos, you know because of her age that only 20% are apt to be genetically normal.” *Dr. James P. Toner*

In IVF, a leading cause of implantation failure and miscarriage is embryonic aneuploidy.<sup>11</sup> Furthermore, euploidy decreases linearly with age (Figure 3), leading to lower IVF success rates.

Embryo selection on the basis of morphology fails to identify aneuploidy. Early approaches to preimplantation genetic screening (PGS) using fluorescence in situ hybridization (FISH) were inaccurate. Another barrier was that biopsy at the cleavage stage significantly reduces the implantation rate.<sup>12,13</sup>

It has now been shown that accurate CCS for all 24 chromosomes can be undertaken at the blastocyst stage using a 4-hour, quantitative polymerase chain reaction method (qPCR).<sup>14</sup> A prospective, blinded clinical study evaluating the predictive value of CCS revealed a very low 4% aneuploidy designation error rate.<sup>15</sup>

Figure 3. Prevalence of euploidy by age

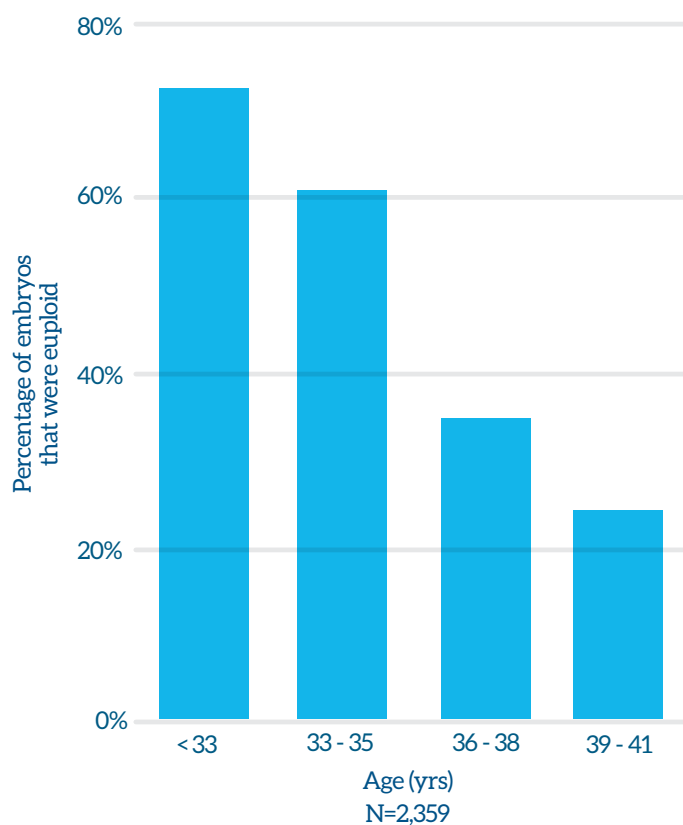
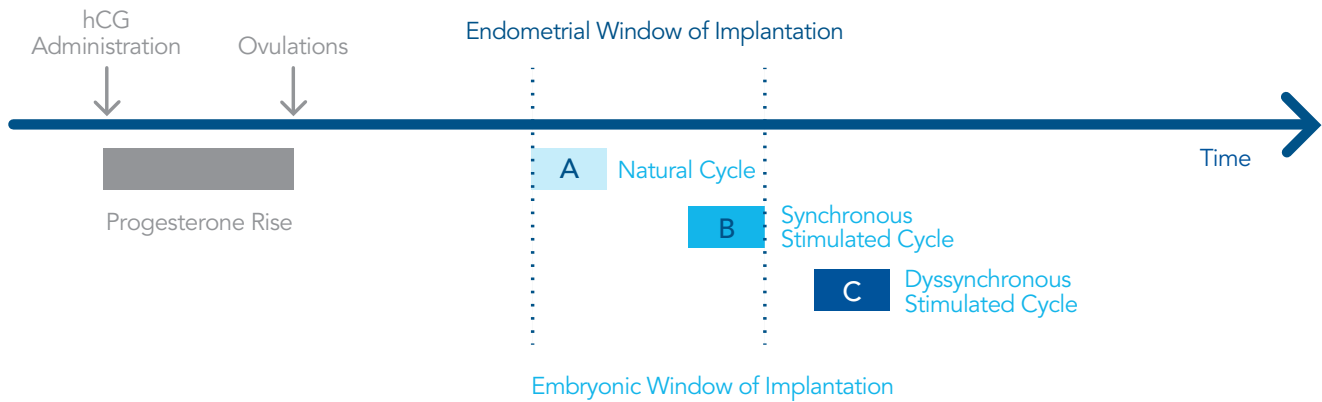


Figure 4A-C. Schematic of relationship between endometrial receptivity and time of blastocyst maturation



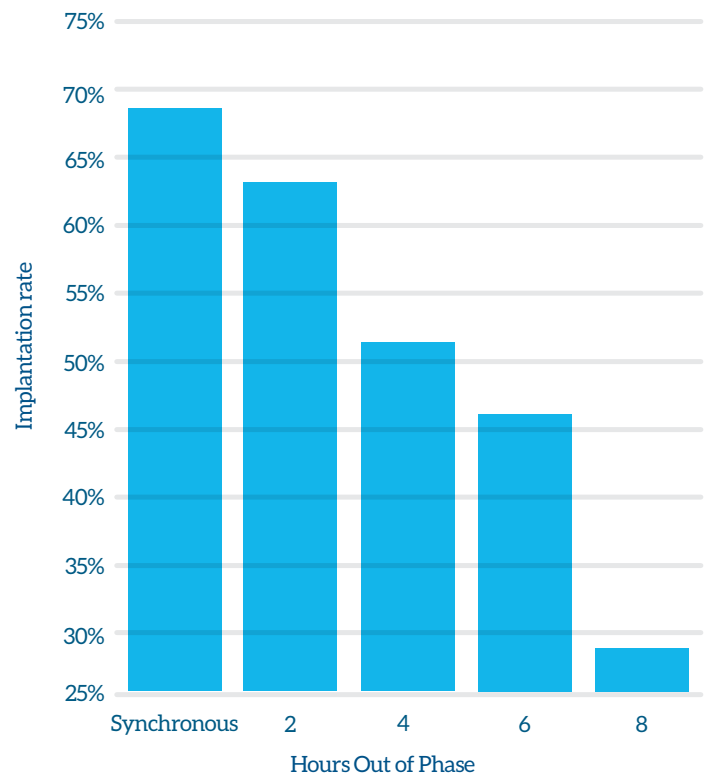
“The ASRM is our guiding professional society. It has been very focused on eSET for women under 35, and I think that is probably not ambitious enough. Even though it is a noble goal, it may not be enough.” *Dr. Richard T. Scott, Jr.*

Successful implantation depends to a large extent on the state of the endometrium and the limited time window during which implantation can occur. During a natural cycle (Figure 4A) the blastulating embryo and endometrial receptivity are in relatively high synchrony owing to ovarian hormones, endometrial factors and embryonic signals.<sup>16</sup> On the other hand, a stimulated cycle may be synchronous (Figure 4B) or dyssynchronous (Figure 4C) because blastocysts vary in their maturation times.

Implantation rates are substantially higher (Figure 5) if the embryo is fully blastulated at the time of transfer to an optimally receptive endometrium. In the US today, more and more IVF programs are able to support embryo development to the blastocyst stage. For example, one of the most recent large, well-controlled, prospective trials demonstrated that 94.6% of patients had at least one transferable blastocyst stage embryo - well over 80% had 2 or more.<sup>11</sup>

Implantation rates decline as dyssynchrony between the embryo and endometrium increases. Advances in vitrification mean that embryos can be cryopreserved for a subsequent cycle in order to optimize synchrony with endometrial receptivity; ongoing pregnancy rates (OPRs) are virtually identical for fresh and frozen transfers.

Figure 5. Implantation rates decline as dyssynchrony between the embryo and endometrium increases





CCS and Trophectoderm Biopsy Improves Blastocyst Stage SET Outcomes

A comparative retrospective analysis of all SETs performed at RMANJ for a specified time period showed that OPRs were significantly higher in women who had undergone SET with CCS (CCS-SET; 55%) than in those who had traditional SET (Control SET; no aneuploidy screening, 41.8%;  $P<.01$ ).<sup>18</sup> For women in the CCS-SET group, the miscarriage rate was 10.5% compared with 24.8% in the Control SET group ( $P<.01$ ). CCS-SET OPRs were higher for all age groups (<35 years to >40 years). OPRs were similar for fresh and frozen transfers.

The Blastocyst Euploid Selective Transfer (BEST) trial, a randomized controlled study, was conducted to establish whether

the transfer of a single euploid blastocyst would provide as good a chance for an ongoing pregnancy as the transfer of 2 unselected blastocysts.<sup>11</sup>

Women (up to age 43 years) were assigned randomly to undergo CCS-SET or morphology-based DET (untested DET); fresh embryo transfer was performed on day 6 if blastulation occurred by late afternoon of day 5. If not, blastocysts were vitrified and transferred at the next cycle.

The proportion of ongoing pregnancies ( $\geq 24$  weeks gestation) was very similar in the 2 groups (Figure 6). Importantly, the 95% confidence interval (CI) of the between-group difference in ongoing pregnancy rate also showed that CCS-SET was not inferior to DET.

“CCS offers exceptional advancements to patients: it reduces risk, improves efficacy, and avoids many miscarriages, which lead to a devastating delay in older women. CCS is really the right tool to build into IVF.” *Dr. James P. Toner*

Figure 6. Ongoing pregnancy rates: CCS-SET versus DET <sup>11</sup>

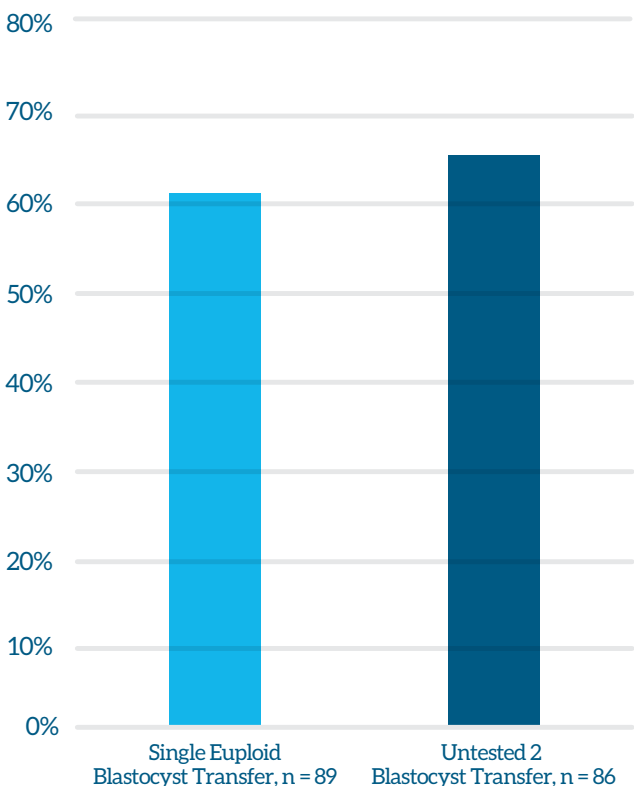
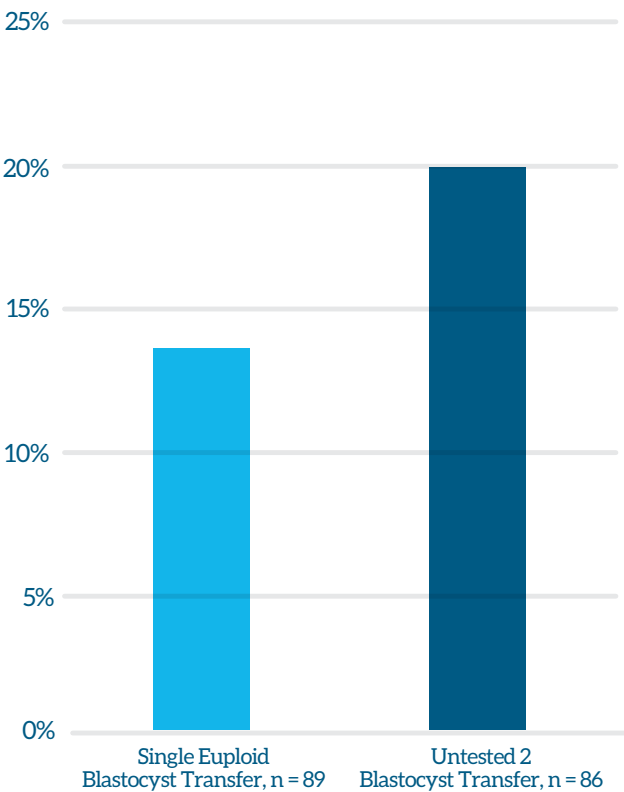


Figure 7. Miscarriage rates <sup>11</sup>



Miscarriage rates were lower with CCS-SET than with DET (Figure 7). The multiple pregnancy rate at discharge to obstetrical care was significantly higher ( $P<.001$ ) in the DET group: 52.4% versus 0% in the CCS-SET group (Figure 8). The likelihood of a single ongoing pregnancy was also significantly ( $P<.001$ ) greater in the CCS-SET than in the DET group (60.7% vs 33.7%, respectively, a nearly 2-fold difference). Taken together, these Class I data from a randomized controlled trial demonstrate clearly that CCS-SET can provide the same ongoing pregnancy rates as untested DET in a single treatment cycle across age groups up to 43 years old. At the same time, this approach dramatically reduces the risk of twins, a major cause of iatrogenic complications in IVF.

It should be noted that **94.6% of patients in the BEST trial produced at least one transferable blastocyst embryo** alleviating concerns that a strategy of blastocyst culture could result in higher cancellation rates for patients. Additionally 86.2% of patients had at least 2 blastocysts including 76.3% who were 38 years of age or older.

Follow-up research of BEST trial patients is now starting to become available and demonstrates the benefits of CCS-SET strategies across a whole range of outcome parameters including risk of NICU admission. (Fig 9) NICU admissions were substantially lower in the SET-CCS group versus the double embryo transfer group demonstrating that excellence clinical outcomes could be achieved with fewer obstetrical complications.

Figure 8. Proportion of multiple versus singleton pregnancies <sup>11</sup>

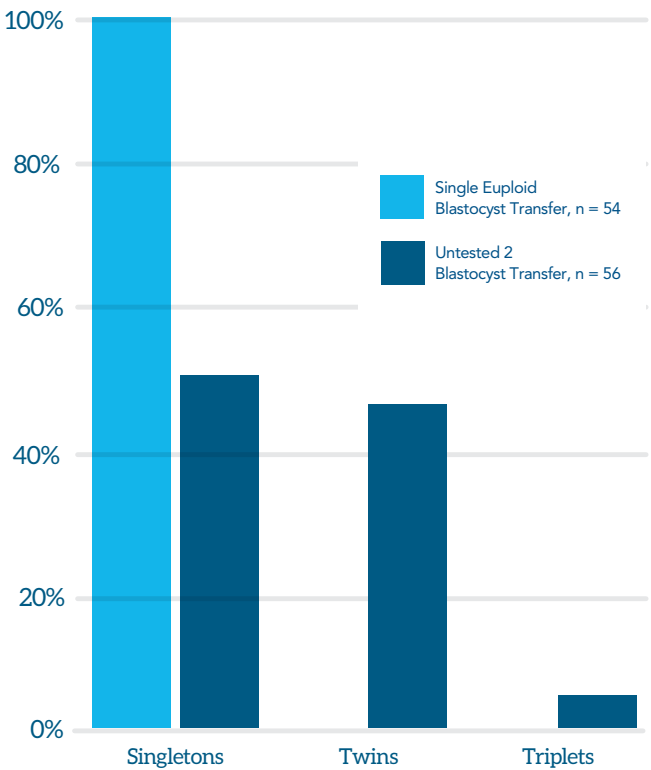
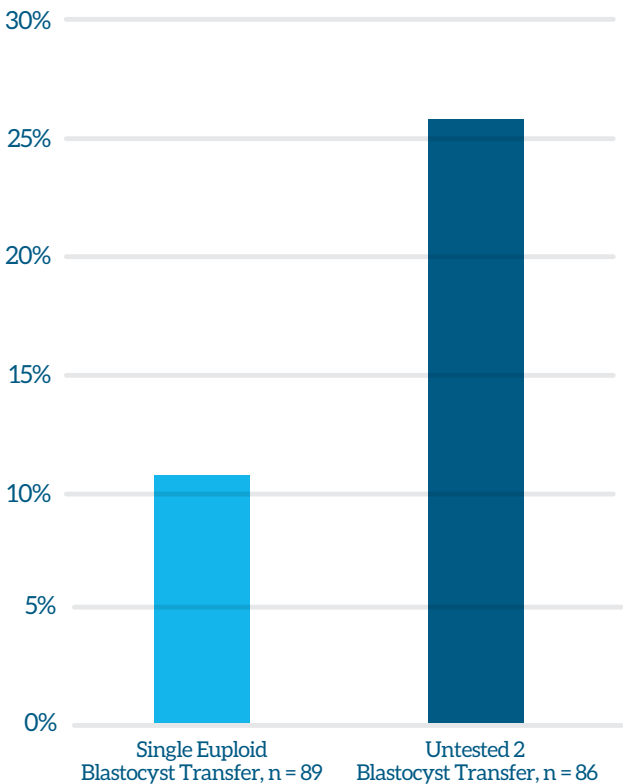


Figure 9. Risk of NICU admission <sup>12</sup>



A woman with blonde hair, wearing a black dress with white floral patterns, is smiling and pushing a grey stroller. Inside the stroller, a young child with blonde hair and blue eyes, wearing an orange patterned shirt and green shorts, is looking directly at the camera. The stroller has a grey and white plaid interior. They are walking on a paved path in a park with green trees and grass in the background. A white car is partially visible on the right side of the path.

# The Pathway to SET

*Stakeholder Perspectives*

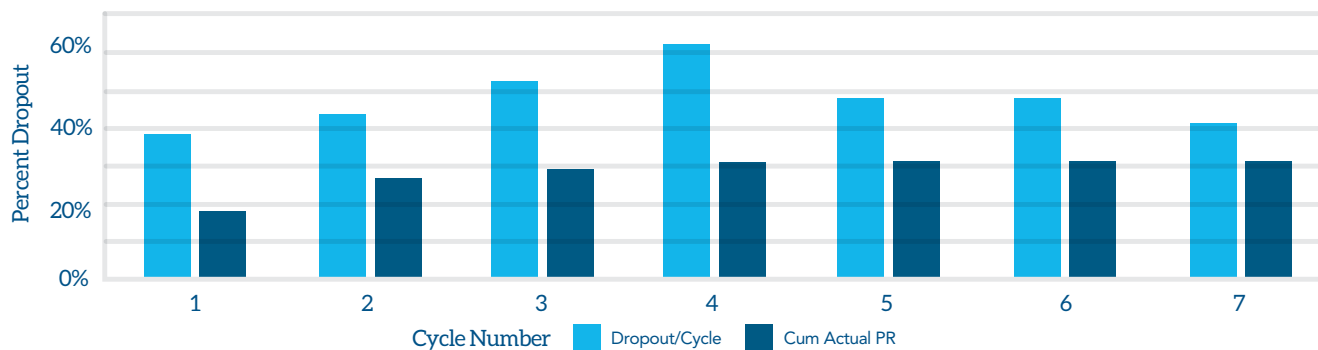
Moving toward SET as the standard of care involves all stakeholders – patients, healthcare providers, and payers, each of whom brings different concerns and considerations to the decision-making process. Dr. Toner added, “We’re certainly helping lots and lots of families have children but to the extent that we could have these children come individually – that is a shared goal.” Meeting participants articulated their concerns and recommendations from varying perspectives. Currently costs fall under different “buckets” between pharmacy and medical benefits. Overall costs of twins may not be evaluated or fully appreciated. As we move to EMR and particularly within integrated systems and ACOs, the opportunity to analyze the impact of SET with CCS vs. DET will be of interest to the entity that is bearing the risk for cost and outcomes and will have interesting policy ramifications for both patients and providers

“As soon as questions of will of decision or reason or choice of action arise, human science is at a loss.”

*Avram Noam Chomsky: From a British television interview (30 Mar 1978) quoted in The Listener (6 Apr 1978)*

For patients, the psychological aspects of infertility and accompanying stress can be overwhelming. The dropout rate from IVF is considerable, with stress playing a major role. (Figure 10)<sup>19-22</sup> Even with 2 to 3 cycles paid, the dropout rate was as high as 60% in a Swedish study, with 26% dropping out because of the psychological burden.<sup>21</sup>

Figure 10. The IVF dropout rate is considerable <sup>19</sup>





The most recent data from a US prospective survey of insured patients showed that stress accounted for 39% of the dropout rate, with the 2 most common causes of stress being the strain on the couple's relationship and high levels of anxiety or depression.<sup>23</sup> Not only patient factors, but the clinical environment and the actual burden of treatment contribute to the dropout rates.<sup>24</sup>

Reducing the impact of each of these aspects of infertility may help alleviate some of the stress of treatment. One option, the increase in the likelihood of success with CCS-SET, may be expected to reduce some portion of the stress.

“When patients come to our center, or any center, they think ‘Well, I’ll have 2 embryos transferred – or I’ll have 3...the default is never single embryo transfer.’ Our goal is to provide the right framework to make the choice between SET and DET.” *Dr. Costantini-Ferrando*

The psychosocial costs in women with a history of infertility can be high; they are more likely to find their parental role challenging and to experience stress and depression along with a generally negative impact on their personal and social lives. Moreover, the impact may be long-term.

Studies have shown that mothers of IVF twins are subject to higher levels of parenting stress and depression than mothers of IVF singletons. One study noted these ill effects were reported when the twins were 2-5 years old.<sup>9</sup> Relative to women with singleton births, they may experience reduced ability to work outside home and a higher rate of divorce, adding to the parental burden. Mothers of low birth weight infants also experience lower levels of attachment to their babies.<sup>25</sup>

Despite these findings, many patients present for IVF with strong expectations of having 2 to 3 embryos transferred. They come with existing psychological comorbidities and, as Dr. Costantini-Ferrando noted in this context they may not be able to differentiate the sources of their anguish and cannot necessarily perceive additive or exponential burdens of multiple births.

Many patients may have a strong desire for twins at any cost because they do not have the ability to do emotional forecasting.<sup>26</sup> They may have financial pressures because of out-of-pocket costs, which they perceive to be best addressed by having at least 2 embryo transfers at the same time and not having to go through the IVF expense again. To them, a multiple birth may be highly desirable as they cannot fully grasp what the costs really will be in terms of additive psychological, physical, or emotional stressors.

For patients in these circumstances, commented Dr. Costantini-Ferrando, “It is not a question of 2 versus 1; it’s a question of 2 versus 0, and they are apt to be ill-informed and ill-prepared for the reality.”

Dr. Costantini-Ferrando also noted that “parents of naturally conceived twins are very different than parents of IVF twins because they’ve reached their goal in a very different way. And so, by the time they even begin to deal with the stress of having twins, of being pregnant with twins, they’ve usually invested a lot less into the process as compared with the couple who achieve twins through ART. As Lee Rubin Collins added. “...and once they have the twins, they feel they can’t complain even if they’re miserable.”

Panelists agreed that from a patient advocacy perspective, it is important to move forward in a way that encourages patients to follow a path leading to the lowest rates of morbidity and mortality. Patient counseling and education is critical to helping patients reduce the cognitive dissonance between their emotions and their intellect. The panel further noted that finding ways to influence the decision making context for patients will most probably lead them to support SET by their having:

- **A better understanding of the morbidity, mortality, and take home baby rate associated with DET v SET**
- **The ability to assess both near-term and long-term resources**
- **The ability to redirect internal drivers of adaptive preference for the DET path**

Research results suggest that current educational efforts and materials in US clinics and elsewhere are lacking in many instances in fully explaining all options.<sup>24</sup> Regarding education, it is also important to consider involving primary obstetrics and gynecology practices, as they are often the first clinician that counsels the woman about ART options.

By the time patients are referred to specialists for some form of infertility treatment, many are already frustrated and stressed. Continuity of educational messages throughout the healthcare system could help establish SET earlier in the process for patients.



## SET - Healthcare Provider Perspectives

Maternal and perinatal health care consequences of twin and higher-order births are high (Table 2 and 3).<sup>1,10</sup> Outcomes of IVF twin pregnancies were associated with significantly higher rates of preterm and very preterm births, low and very low birth weights, and small for gestational age as compared with outcomes of IVF singleton. Adjusted odds ratios ranged from 4 to 16.

In this same cohort, neonatal morbidity was also greater, with significantly higher rates of respiratory complications, sepsis, and jaundice among IVF twins.

Maternal outcomes were also significantly worse in twin IVF pregnancies compared with IVF singleton pregnancies with higher rates of preeclampsia, preterm premature rupture of the membranes, and cesarean section.<sup>27</sup>

These data are consistent with other studies among non-IVF obstetric populations showing higher rates of major maternal complications with multiple pregnancies.

Table 2. Incidence of major maternal complications in multiple pregnancies<sup>1</sup>

	Singleton	Twin	Triplet	Quadruplet
Preeclampsia	6	10 - 12	25 - 60	>60
Gestational diabetes	3	5 - 8	7	>10
Preterm labor	15	40	75	>95
Delivery at <37 wk	10	50	92	>95
Delivery at <32 wk	2	8	26	>95

Practice Committee, Multiples, Fertil Steril 2012

Table 3. Neonatal outcomes in twin versus singleton IVF pregnancies

	Twin	Singletons	Siblings
Total infants	1,982	1,842	17 (0.9)
< 37 wk	925 (46.7)	133 (7.2)	2 (0.1)
< 32 wk	148 (7.5)	23 (1.2)	9 (0.5)
< 2,500 g	769 (38.8)	85 (4.6)	2 (0.1)
< 1,500 g	106 (5.3)	24 (1.3)	1 (0.1)
Small for gestational age	246 (12.4)	43 (2.3)	0 (0.0)
Peri/neonatal mortality	23 (1.2)	18 (1.0)	
Apgar < 7 <sub>5</sub>	59 (3.0)	30 (1.6)	
Severe neonatal morbidity			
Relatively severe malformations	97 (4.9)	70 (3.8)	
Respiratory disorders	322 (16.2)	83 (4.5)	
Meconium aspiration	1 (0.1)	4 (0.2)	
Bronchopulmonary dysplasia	12 (0.6)	5 (0.3)	
Intraventricular hemorrhage (≥ grade 3)	4 (0.2)	1 (0.1)	
Convulsions	4 (0.2)	6 (0.3)	
Periventricular leukomalacia	4 (0.2)	0 (0.0)	
Hypoxic - ischemic encephalopathy (≥ grade 3)	1 (0.1)	1 (0.1)	
Retinopathy of prematurity	13 (0.7)	2 (0.1)	
Retinopathy of prematurity (≥ grade 3)	5 (0.3)	0 (0.0)	
Sepsis	45 (2.3)	20 (1.1)	
Necrotizing enterocolitis	3 (0.2)	0 (0.0)	
Jaundice	381 (19.2)	90 (4.9)	
Stillbirth and infant mortality <1y	27 (1.4)	18 (1.0)	
Composite serious morbidity <sup>b</sup>	45 (2.3)	23 (1.2)	

<sup>b</sup>Composite serious morbidity: bronchopulmonary dysplasia, intraventricular hemorrhage ≥ grade 3, periventricular leukomalacia, hypoxic-ischemic encephalopathy ≥ grade 3, retinopathy of prematurity (≥ stage 3), necrotizing enterocolitis, stillbirth, and infant mortality <1 year.  
Sazonova. Twins and singletons after IVF. Fertil Steril 2013

The panel noted that while maternal and perinatal morbidity issues are key, these outcomes generally lack comprehensive and integrated descriptors. The group suggested the need for better definitions of negative outcomes from IVF pregnancies, for example by creating a standardized and common language for obstetric outcomes and defining levels of care.

They also identified some steps and actions that could assist in the adopting of SET as a standard of IVF care. These included:

- **Collection of longer-term outcome data from a multicenter, multistate trials**
- **Ensuring accessibility of the SET technology to both providers and patients, perhaps through creation of centers of excellence, shared technology, and central laboratories; any such actions would need to address patient access because of regional differences in health care**
- **Developing training programs to teach the SET techniques to a broader range of providers**

Dr. Barth again emphasized that an intervention that can reduce twinning is a huge advance because preterm birth is the single major cause of neonatal morbidity and mortality. Moreover, a very recent study that examined the association between gestational age and development status at 1 year of age, showed that for each additional week of gestation, development scores increased.<sup>27</sup>

It has become increasingly clear that combining CCS, trophoctoderm biopsy, endometrial synchrony, and SET can be the pathway to reduce the risks of multiple births in IVF. Because this approach can substantially alter the odds of twinning while increasing the success rates for a single healthy baby, it is a paradigm of care that should be critically considered. The panel agreed that guidelines and mandates could help change practice patterns, especially when these practice patterns are backed by data and not opinion.

“Speaking as a perinatologist, anything from the reproductive endocrinology side of our discipline that recognizes the morbidity associated with multiple gestations and tries to decrease that, should be applauded.” *Dr. William Henry Barth, Jr.*

Not only should education be directed at patients about IVF choices open to them, but healthcare providers should also be provided with data regarding the benefits of SET.

The barrier created by the patient mindset that IVF twins are desirable will require comprehensive education. In an examination of strategies to reduce multiple gestations and births resulting from IVF, Dr. Scott reviewed data from infertility patients who were physicians. In a subset of obstetrician/gynecologists and specialists in maternal/fetal medicine physicians, he found that not a single one chose SET out of more than 200 cycles of care. These data highlight the importance of recognizing and addressing the emotional and psychological context in which education and counseling take place.

Physicians and other healthcare providers should address the issue of what truly constitutes informed consent in this situation. Often, patients do not see themselves in population-based terms and may not consider concepts of relative and absolute risks. Currently, it is not possible to predict if twins will be born prematurely. As Dr. Yeomans clearly stated, “The main complication for twins is preterm birth, and our ability to predict preterm birth in someone with a negative history is not very good.”

Another issue is to reconfigure how success rates are reported by clinics. As Dr. Toner noted, “If our pregnancy rates drop 10 or 15%, that will be challenged in the short-term; but it’s important to understand that it’s the right thing to do.” With SET, this should not be a concern, since data from a well-controlled, randomized study show that the technology available now can provide pregnancy rates as high as DET and possibly higher than the current national average.

The data also demonstrate that screening embryos for euploidy can help overcome issues associated the increasing proportions of abnormal eggs that occurs with age and therefore the increased likelihood of miscarriage.

Further, the use of the approach above has been adopted by centers nationally, showing that it can be applied more widely throughout the US. In 2012, 52% of CCS cases performed by RMANJ were completed for 9 other IVF programs in the US, indicating that diffusion of techniques and technology is now happening.<sup>28</sup> The challenge now is to ensure that validated and effective technologies become even more widely available.

## Payer Perspectives

Although data from cost-effectiveness studies can be complicated and difficult to interpret because of varying definitions of outcome measures and the types of comparisons that are undertaken, costs of IVF twin pregnancies are substantially higher than singleton pregnancies, involving higher rates of cesarean section, length of maternal hospital stay, length of neonatal intensive care unit (NICU) stay and non-NICU length of stay (Table 4).<sup>29</sup>

Meeting participants agreed that existing data, regardless of study limitations, consistently demonstrate the considerable direct and indirect costs of IVF twin births and suggested that these are likely to be understated. Moreover, long-term costs and impacts on the family units, society, and health outcomes have not been adequately studied.

The dearth of data may be remedied when the results of a long-term study, called the TwinSing study, become available. This study aims to evaluate the effects of SET to reduce IVF twin pregnancies on long-term costs and outcomes for up to 5 years.<sup>9</sup> Similar data from the United States are not likely to become available in the foreseeable future.

“Maternal fetal medicine specialists are going to be very strong advocates for reducing the multiples from ART but convincing patients and exporting the laboratory expertise are a couple of the biggest hurdles that we face today.” *Dr. Edward R. Yeomans*

Table 4. Data on antenatal care and delivery per pregnancy<sup>29</sup>

	Singleton Pregnancies	Twin Pregnancies
<b>Antenatal Care (%)</b>		
Midwife	28 (20.7)	0
Hospital (gynecologist/midwife)	107 (79.3)	144 (100.0)
<b>Delivery (%)</b>		
Vaginal uncomplicated	88 (65.2) <sup>3</sup>	0
Vaginal complicated	20 (14.8)	87 (60.4)
Cesarean section	27 (20.0)	57 (39.6)
<b>Maternal Admission (%)</b>		
Length of stay <sup>b</sup> (days)	3.6 (2.2)	10.1 (1-59)
<b>NICU Admission<sup>c</sup> (%)</b>		
Length of stay <sup>c,b</sup> (days)	0.11 (0 - 11)	1.8 (0 - 42) <sup>d</sup>
<b>Non - NICU Admission<sup>c</sup> (%)</b>		
Length of stay <sup>c,b</sup> (days)	2.0 (0 - 33)	8.8 (0-42) <sup>d</sup>

\* Including 13% (n=18) home deliveries; Values are means (range). • Calculated per newborn; Six weeks (42 days) was maximum length of follow-up

Note: NICU = neonatal intensive care unit.

“Reducing the possibility of multiple births has such great merit – just to limit the number of twin gestations that come out of IVF.”

*Dr. Edward R. Yeomans*

“The concept of spending less money for better care with better outcomes is at the heart of quality improvement. As science evolves, value should be what we all strive for and need better alignment between payers, providers and patients.” *Dr. Maria Lopes*

Authors of a recent essay in the Hastings Center Report argued in favor of paying for all fertility treatment based on ethics and policy.<sup>2</sup> They too, however, recognized the emerging consensus on the adverse maternal and neonatal outcomes of multiples, including twin births, as a negative outcome of infertility treatment, clinical practice in the US remains oriented toward standards that are likely to produce twins. They raised the issue of whether this is the result of careful weighing of risks and benefits on the part of physicians and their patients and representative of true informed choice.

They argued that patient preference for 2 babies from 1 pregnancy is likely to be heavily influenced by cost concerns, stating, “It is quite possible, we believe, that these cost concerns actually undermine the autonomy of fertility patients, pushing many of them to take risks with their health and the health of their hoped-for future children” - a situation they recognized as “ethically problematic.”<sup>2</sup>

Meeting participants addressed the issue of what it would take to change how the ways in which the costs of infertility are reimbursed. Currently, costs fall into different “buckets” so the overall costs of complications resulting from twin pregnancies may fall into different cost centers. This means that the true costs cannot be assessed or appreciated presently. As Dr. Lopes noted, “Electronic health records and birth certificates are really the way of the future. And this is an opportunity for an integrated system, to look at total costs from IVF from all medical sources.”

Although there is considerable literature on the costs of multiple pregnancies, participants also felt strongly that there is discrepancy between available data and actual direct and indirect costs. Identified sources of cost run the gamut from pregnancy complications, miscarriage, preterm delivery, perinatal morbidity and mortality, and possibly lifelong impairments. New metrics are needed to evaluate these costs.

Other identified needs included ways of addressing state versus federal regulations, development of strong, evidence-based practice guidelines that payers can use to implement policies, the importance of data demonstrating cost-effectiveness of SET and vitrification over other options, and considering the impact of insurers implementing policies that would pay more on the front end in order to save money downstream.





It was agreed that coverage for SET versus DET would help impel a shift in the standard of care, as demonstrated by a recent policy statement by Aetna, characterized as improving chances of conception and increasing maternal and infant safety (Table 5).<sup>31</sup>

The policy addresses the increased risks and costs of multiple gestations, including:

- **Increased rates of premature birth and cesarean section delivery**
- **Increased rates of NICU utilization**
- **Additional medical care needs in the first year of life and increased needs beyond the first year**

In the United States, 62% of ART twins and 97% of ART triplets were delivered preterm with the annual financial burden of ART-associated preterm deliveries totaling approximately \$1 billion USD in 2006.<sup>30</sup>

Table 5. The **aetna** Example

 <p><b>Institutes of Excellence®</b></p> <ul style="list-style-type: none"><li>• Access to a network of top-performing infertility clinics.</li></ul>	 <p><b>National Infertility Unit</b></p> <ul style="list-style-type: none"><li>• Access to a dedicated Aetna clinical team experienced in infertility care and coordination care</li></ul>
 <p><b>eSET - for women under 35 years of age who have not failed an IVF cycle</b></p> <ul style="list-style-type: none"><li>• The option to undergo an additional cycle with a frozen embryo</li><li>• This will not count against the IVF benefit limit</li></ul>	 <p><b>Provisions of an online educational video series developed by the CDC</b></p> <ul style="list-style-type: none"><li>• Wellness and preconception tips</li><li>• Clinical outcomes of infertility provided (compiled by CDC)</li><li>• Benefits of eSET</li><li>• Questions to discuss with physicians</li></ul>

“The bottom line is to achieve the best pregnancy success rate, reduce multiple births, and thus help lower all associated costs.”


Dr. Maria Lopes



A man and a woman are sitting on a white shaggy rug in front of a large window. The woman, on the left, has long brown hair and is wearing a purple cardigan over a white top. She is holding a tablet. The man, on the right, has short brown hair and is wearing a grey button-down shirt and blue jeans. They are both smiling and looking at the tablet. The background shows a bright window with white curtains and a view of a red building outside.

# The Pathway Forward

*Implementation Recommendations for SET*



Despite advances in fertility treatment and success rates, multiple gestations remain the single most important complication of IVF cycles that result in a birth. Nevertheless, the technology is at hand, backed by high level evidence, to move toward a new standard of care – one that includes enhanced embryo selection for SET through trophoctoderm biopsy and aneuploidy screening, attention to optimal windows of endometrial receptivity, and vitrification when necessary.

“The technology is available today to make SET a reality and IVF safer for mom and the baby. The time is now to avoid all multiple pregnancies.” *Dr. Gloria A. Bachmann*

Enhanced delivery rates in fewer treatment cycles with reduction in the risks of multiple gestations is now a reality. Transferring 1 embryo with screening is as good as transferring 2 without screening. Experts representing key stakeholders in the field of infertility provided their unique perspectives on current standards and the pathway forward. Making SET the standard of care can be fostered if disciplines align and integrate their efforts through multifaceted channels including:

- Public health campaigns to raise awareness about the risks of multiple gestations and the strong scientific evidence in favor of a paradigm shift
- Ongoing research to document and extend outcome optimization to more centers
- Publication of data in mainstream medical journals to reach beyond infertility specialists and to ensure that community obstetrician/gynecologists have the knowledge they need about SET to help set realistic patient expectations for one healthy baby at a time
- Strengthening of professional, evidence-based guidelines, coupled with payer reform to integrate costs from front end onward
- Standardizing outcome descriptors to clearly differentiate clinical pregnancy from live birth
- Implementation of advocacy, counseling, and education to reduce the current dissonance between emotional decision-making and optimal health choices among patients
- Providing uniform standards for patients and other stakeholders to evaluate fertility centers for state-of-the-art practices (Table 6)

Table 6. Standards for Infertility Centers



- ✓ IVF delivery rates at or above the national average, combined with regular use of single embryo transfer
- ✓ Routine use of genetic screening with validated technologies
- ✓ Trophectoderm embryo biopsy only
- ✓ Embryo culture to blastocyst stage for most or all patients
- ✓ Evaluation of endometrial synchrony during blastocyst transfer; cryopreservation in the event of dyssynchrony
- ✓ Limited use of double embryo transfer with virtually no triplet rates

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