

THE USE OF ELECTIVE SINGLE EMBRYO TRANSFER (eSET) TO REDUCE THE RISKS
OF MULTIPLE GESTATION

By

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TABLE OF CONTENTS

Abstract	3
Introduction	3
Methodology	12
Interview 1	14
Interview 2	22
Interview 3	28
Results	34
Discussion	37
References	42

ABSTRACT

In vitro fertilization (IVF) is a common method used in assisted reproductive technology (ART) to help patients achieve pregnancy. One of the risks of IVF is the possibility of multiple gestation, especially when more than one embryo is transferred per cycle. Multiple gestation can introduce several significant complications into the pregnancy and birth, which can range from short-term conditions to long-term disabilities. Elective single embryo transfer (eSET) is a way of reducing these risks by choosing to transfer only one embryo when multiple embryos are available for transfer. With eSET, the chances of multiple gestation and its associated complications are significantly lowered, increasing the chances of the patient having a healthy pregnancy. However, eSET appears to have low rates compared to other methods of transfer, despite its benefits. This thesis investigates the use of eSET in fertility clinics, in order to gain insight on the level of patient awareness on eSET, how fertility clinics provide eSET, and methods that can encourage patients to choose eSET. Physicians at fertility clinics will be interviewed, and the interviews will be used to analyze how to improve the rate of eSET and reduce the rate of multiple gestation in fertility treatments.

INTRODUCTION

The use of assisted reproductive technology (ART) to help patients achieve pregnancy has been around for quite a while, yet even now there are still new procedures and techniques being studied. ART can always use improvement, especially to reduce the risks associated with certain methods. One such risk of ART is multiple gestation, where a patient is pregnant with multiple fetuses. On average, multiple-fetus pregnancies occur in approximately 26.9% of ART cycles that resulted in pregnancy (“2014 Assisted Reproductive Technology National Summary

Report”, 2014). Multiple gestation introduces several risks to both the fetuses and the mother. However, elective single embryo transfer (eSET) is a method that can reduce the chances of multiple gestation and its associated risks.

The most common procedure used in ART cycles is in vitro fertilization (IVF), which accounts for more than 99% of ART procedures. IVF is an ART technique where the sperm and egg are removed from individuals to be combined manually outside the body and transferred back into the patient’s uterus. First, ovarian stimulation is achieved by giving high doses of FSH to patients for several days during the follicular phase to develop multiple follicles in the ovaries. GnRH antagonists are administered during the last 4 days of ovarian stimulation, resulting in suppression of LH production to inhibit early ovulation (Stillman, Richter, Banks, & Graham, 2009). 36 hours prior to egg retrieval, hCG is administered to mimic the LH surge that triggers final egg maturation (Stillman et al., 2009). The eggs are removed from ovaries 34 hours after hCG administration using transvaginal ultrasound aspiration, a process that involves using a needle to aspirate eggs out of follicles with the guidance of ultrasound under anesthesia. The eggs are then fertilized through intracytoplasmic sperm injection (ICSI), where a single sperm is directly injected into an egg to create a zygote.

Embryos are cultured in media, either to day 3 cleavage-stage or to day 5 blastocyst-stage. Most non-randomized studies have found that transfer of either type of embryo has resulted in very similar pregnancy rates (Stillman et al., 2009), although one such study with selected patients has suggested that day 5 blastocysts have higher implantation and live birth rates compared to day 3 embryos (Adamson, 2015).

For fresh embryo transfer, the most common process is for multiple embryos to be transferred to the uterus through a catheter. However, transfer of more than one embryo comes

with risks related to multiple births. Several studies have described the negative consequences associated with multiple births. The main risks are prematurity, which results in increased infant mortality, lower birth weight, intraventricular hemorrhage, enterocolitis, respiratory distress syndrome, and sepsis in the newborn (Gerris & Sutter, 2009). There has been an increase in childhood complications from neurological, ocular and pulmonary damage, learning disabilities, and congenital malformations resulting from premature multiple births (Stillman et al., 2009). Multiple births are associated with higher risks of cerebral palsy, birth defects, autism spectrum disorders, and other long-term complications (Kissin, Boulet, & Adashi, 2015). Multiple births also have higher risks of miscarriage and neonatal death, up to 6 times higher in twins and 14 times higher in triplets than in singletons (Kissin et al., 2015).

There are also other risks that are for the mother, including medical, financial, and psychological factors. Maternal risks include higher chances of pre-eclampsia, gestational diabetes, myocardial infarction, venous thromboembolism, pulmonary edema, postpartum hemorrhage, caesarean section, morbidity, and mortality (Gerris & Sutter, 2009; Stillman et al., 2009). There are significant financial costs to caring for children of multiple births, which also includes the cost of delivery and neonatal care for the newborns (Gerris & Sutter, 2009; Stillman et al., 2009). Also, parents of multiple births have often found themselves to be undergoing severe emotional stress and mental health consequences, which may be contributed to by any developmental disabilities or long-term complications associated with multiple birth (Gerris & Sutter, 2009; Kissin et al., 2015).

Prematurity occurs at much higher rates in multiple births than in singleton births, with incidence rates of 6-7% for singleton births, over 50% for twin births, and over 90% for higher-order multiple births (Gerris & Sutter, 2009). Overall, ART contributes to only 1.5% of live

births in the U.S., but to 4% of all preterm infants (Kissin et al., 2015). This weighted effect suggests that there is a significant issue with ART resulting in premature births and increasing the risks associated with prematurity.

Elective single-embryo transfer (eSET) has been proposed as an effective method for reducing multiple births in IVF and preventing many of these risks. eSET is the decision to transfer one embryo even though more than one embryo is available for transfer (Kissin et al., 2015). Of the multiple embryos, at least two or more must be high-quality blastocysts (Stillman et al., 2009). This distinguishes eSET from other types of single-embryo transfer, such as compulsory or medical. Compulsory SET differs from eSET in that only one embryo is suitable for transfer after retrieval and culture, and it may be of poor-quality with a low anticipated implantation rate (Gerris & Sutter, 2009). Medical SET is indicated for patients who have increased risks associated with multiple pregnancy. Patients who have a medical history of uterine anomalies, previous premature births, or severe systemic disease are highly recommended to transfer only one embryo at a time to avoid even more harsh complications than normal (Gerris & Sutter, 2009). eSET means that there is a choice from multiple embryos suitable for transfer, and only one embryo is chosen for transfer.

While only half of multiple (MET) or double embryo transfers (DET) result in singleton births, eSET results in 98.3% of births being singletons. This greatly reduces the aforementioned risks of multiple births, as well as significantly reduces the number of premature births so that 88.1% of eSET births happen after 37 weeks compared to only 64.1% of DET and 51.1% of MET births (Kissin et al., 2015).

eSET may sound like a tempting option for those looking into reproductive assistance, but surprisingly the percentage of eSET out of cycles involving fresh embryos from non-donor

eggs was only 17.2%, according to the 2014 National Summary Report on ART from the Centers for Disease Control and Prevention (CDC). Despite the benefits that eSET provides in comparison to MET or even DET, it appears that this strategy is not utilized very often. What could be some of the reasons behind this low rate?

Since only one embryo is being transferred in eSET, the issue comes up of whether pregnancy rates will be as successful as when multiple embryos are transferred. One 6-year study by Stillman, Richter, Banks, and Graham found that their pregnancy rates for autologous, own-embryo eSET (65%) were similar to pregnancy rates for DET (63%), whereas donor egg recipients had improved pregnancy rates for DET (74%) compared to eSET (63%) (Stillman et al., 2009). However, other research suggests that eSET results in significantly lower pregnancy rates (Adamson, 2015), while still other research suggests that eSET does result in lower pregnancy rates, but not with statistical significance (Gerris & Sutter, 2009). The results seem to conflict with each other, making it hard to conclude whether eSET has a negative impact on pregnancy rate. More definitive research on the pregnancy rates of eSET and DET may need to be done to get a better comprehensive comparison.

One way of looking at pregnancy rates is to also assess the factors associated with comparison of embryo quality. eSET is often performed by choosing the highest quality embryo with the use of blastocyst biopsy, pre-implantation genetic screening (PGS), or visual observation (Laver, Abdo, Kotrotsou, Trew, Konstantinidis, & Wells, 2012). eSET may then be comparable to indiscriminate two-embryo transfer, where the quality of the embryos transferred may be high or low (Gerris & Sutter, 2009). High success rates of transferring two high-quality embryos are offset by low success rates of transferring two low-quality embryos, which could explain a balanced pregnancy rate similar to the eSET pregnancy rate (Gerris & Sutter, 2009).

Studies that then selectively choose two high-quality embryos for transfer will indeed have higher pregnancy rates than transferring one high-quality embryo in eSET, but acquire even higher risks of multiple gestation and birth (Gerris & Sutter, 2009). To try and balance transferring multiple embryos for a higher pregnancy rate with lower risks of multiple birth is highly unlikely.

Another issue is creating a set of requirements for patients who are the best fit for eSET. Patients commonly recommended for eSET are younger than or equal to 35 years of age with good embryo quality (Stillman et al., 2009). Studies show that eSET for patients in their late 30s or higher had a moderate decrease in success (Stillman et al., 2009). When age is taken into account, the percentage of eSET used in cycles of fresh embryos from non-donor eggs is now 28.5% for patients below 35 years, compared to the 17.2% rate for all ages. Overall, eSET is recommended more for patients under 35, who are more likely to have higher embryo quality.

Advanced maternal age makes it harder to achieve a healthy singleton birth with eSET, so only patients who are younger than 35 years of age with favorable prognosis or 35-37 years of age with available blastocyst-stage embryos are normally considered for eSET (Kissin et al., 2015). Favorable prognosis means that these patients are usually undergoing their first ART cycle, have extra cryopreserved embryos, or have blastocyst-stage embryos (Gerris & Sutter, 2009; Kissin et al., 2015). For older patients, it is more likely that donor eggs will be more successful, since implantation rate will depend on donor age rather than maternal age. They may also be considered for eSET even if they do not fulfill the age criteria if they have available blastocysts for transfer and have undergone prior IVF treatment. However, the effect of maternal age on pregnancy rate still needs to be taken into consideration, and patients may consider using donor eggs rather than their own.

With the requirements for age and embryo quality, the candidate pool for eSET is narrowed even further. According to the CDC, 57.4% of cycles with fresh embryos from non-donor eggs involved patients 35 years or older (“2014 Assisted Reproductive Technology National Summary Report”, 2014). That leaves only 42.6% of patients younger than 35 years, who can be considered as candidates for eSET. With the addition of older candidates who may not fit the criteria but can still be recommended for eSET, the percentage may be a little higher. However, 42.6% of total patients being possible candidates may explain why only 17.2% of total patients actually choose to do eSET. What this really means is that about 40% of recommended patients choose eSET, a much better outlook than only 17.2% of all patients choosing to do eSET.

Still, fewer than half of recommended patients choosing eSET is rather low. What other factors could also come into play even for good eSET candidates? Perhaps the criteria for patients could be widened and refined if PGS was used to ensure that patients had high-quality embryos available for transfer (Laver et al., 2012). More older patients could also be included with the use of PGS, increasing the percentage of eSET. However, a more important and likely more relevant issue is the patient’s financial situation. Many patients may want to decrease treatment costs and are more likely to transfer multiple embryos in one cycle to avoid paying for repeated transfers if only transferring one embryo does not work (Stillman et al., 2009). Patients might also be considering the wait time if a transfer doesn’t work, since they would have to wait another month or two before they can attempt another transfer.

Despite the long-term financial consequences of multiple birth, it seems as though the costs of paying for more than one transfer is a more influential justification behind multiple embryo transfer. The lack of insurance coverage is another driving factor behind the low eSET

rate. In the U.S., most insurance plans do not cover IVF treatment (Sherbahn, n.d.), putting even more pressure on patients to ensure that their IVF treatment is a success without having to spend more money on extra transfers.

The study by Stillman (2009) also evaluated how reducing financial pressures could affect patients' decisions to choose eSET. The study provided a program that only required an initial fee without additional costs for medical services for up to six full cycles of IVF. Their results showed that the program eliminated patients' financial reasons for transferring multiple embryos to maximize success, and instead led patients to choose eSET at higher rates than patients who paid for each cycle themselves. They concluded that without the immediate financial pressure of paying for all the possible cycles needed in eSET, patients are more likely to choose eSET and avoid the risks of multiple pregnancy. However, this was a program implemented during a study, and not an available option for all patients undergoing IVF. In reality, patients may not have options like these from insurance companies or individual clinics that would allow them the freedom to choose eSET.

One last issue regarding the relatively low percentage of eSET amongst fresh embryo cycles is patient education. How much do patients know about elective single embryo transfer, if they even know about it at all? Do they know about the consequences of multiple birth, and would they choose otherwise if they knew? Although eSET may be recommended as often as possible, patients have to agree to eSET of their own accord. This includes educating patients on the serious physical, psychological, and financial risks of multiple pregnancy and birth, introducing the idea of eSET and the benefits it can provide, and respecting each patient's individual concerns about eSET or IVF (Adamson, 2015; Stillman et al., 2009). Patients who are willing to transfer multiple embryos to ensure successful IVF may not know about the associated

risks of multiple pregnancy, or if they do know about the risks and decide to use MET anyway, may not know that eSET has been shown to provide similar pregnancy rates in several studies (Stillman et al., 2009). Prior studies indicate that through education about the risks of multiple pregnancy, more patients will be inclined to choose eSET and desire multiple pregnancy less (Adamson, 2015; Stillman et al., 2009). The study by Stillman (2009) noticed a correlating increase in the proportion of eSET cycles with the efforts to educate patients about eSET, which suggests that informed knowledge may have influenced patients' decisions.

The goal of this thesis is to examine the use of eSET in specifically fertility clinics, while looking at possible ways to improve the rate of eSET through fertility clinics. This thesis is investigating the level of patient awareness and education of eSET, how fertility clinics may present or provide eSET to patients, and additional methods that can be implemented in fertility clinics to improve eSET rates. This thesis hypothesizes that raising patient awareness about the circumstances of using eSET during IVF and working with fertility clinics to provide patients with varying options concerning eSET can increase eSET rates in fertility clinics and lower the risks of multiple pregnancy for these patients.

METHODOLOGY

Physicians at fertility clinics were interviewed about several issues concerning eSET use in fertility clinics. The questions investigated whether different fertility clinics offer eSET as an option, how much patients know beforehand about eSET, how fertility clinics provide information about eSET, what patients choose to do regarding eSET, and what circumstances may lead patients towards making their decisions. The questions are listed below:

- Does the clinic offer eSET as an option?
 - (if yes) When did the clinic begin offering eSET? How has the usage of eSET here changed over time?
 - (if no) What are the reasons for not offering eSET? Would the clinic ever think about offering eSET in the future?
- Do patients who undergo IVF know what eSET is beforehand?
 - (if some do) Where do they find out about it?
 - (if some don't) How many patients only hear of it through clinical recommendation?
- How often does the clinic recommend eSET to patients undergoing IVF?
- What are the clinic's requirements on patients who can do eSET?
- Are there patients who bring up eSET as an option on their own?
- Are there certain circumstances where eSET would not be recommended?
- After recommending eSET to patients, do they usually follow the recommendation?
- If patients refuse eSET, what reasons do they give for doing so? What are some of the more common reasons?

- Are there patients who refuse eSET because they deliberately want twins or triplets?
- Would a lack of awareness of multiple gestation risks among patients contribute to low rates of eSET?
- What are patients normally told about the possibility of multiple gestation?
- Does pre-implantation genetic screening affect eSET rates?
- Does the clinic offer any financial incentive for choosing to do eSET?
 - (if yes) How does this effect eSET rates for the clinic?
- Does the clinic offer information or pamphlets about eSET? Are there any websites, books, or other information sources recommended for patients?
 - (if yes) Do these information sources increase awareness about risks of multiple gestation and the benefits of eSET?
 - (if no) Would the clinic be open to suggestions for information sources or pamphlets?

3 fertility clinics were interviewed over the course of the study. The interview process was approved by the University of Arizona Institutional Review Board (IRB). The clinics were chosen from the Tucson and Phoenix area in Arizona. The physicians involved in the study are volunteers who signed consent forms. The physicians were interviewed for approximately 15-20 minutes each in an isolated setting. The study was described to the physicians first prior to the interview. The interviews were conducted in a question-answer format, with the physicians allowed as much time as needed to answer each question. The interviews were recorded using the Apple iPhone app Voice Recorder by TapMedia Ltd. During the course of the interviews,

other questions related to the topic but not listed above were also asked. The interviews were then transcribed in order to make analysis easier.

The interviews were transcribed as closely as possible, with the omission of non-distinguishable words or sounds. The transcriptions of the interviews are included below, in no particular order. The physicians have been kept anonymous as per IRB regulations.

The transcriptions were used as a basis for examining patient awareness of eSET and usage of eSET in clinics. However, there are still limitations. The interviews were restricted to the Tucson and Phoenix areas, which may not apply to fertility clinics in other cities or states. The open format of the interview meant that some questions may have been asked for a certain physician that were not asked of the others. Although the interviews were transcribed as accurately as possible, there may still be some mistakes with the transcription. Physicians may also have interpreted the questions differently, and given a variety of answers based on their interpretation.

Interview 1

Q: When did you start offering eSET as an option in your clinic and how has your usage of eSET changed over time?

A: We started doing eSET 5-6 years ago for people who had a high probability of getting pregnant. Under age 35 and with really good blastocysts. And back then, it was mostly fresh embryo transfers, and so that's all changed. The hormone environment from IVF, when you're trying to make a whole bunch of eggs, is so deleterious to the uterine lining that fresh embryos

don't get very good placentation. They don't get a very good placenta. There's pretty good human data as well as animals that you don't get as good a placental invasion, so the babies are born earlier, by about a week or two. So now everything is going to frozen transfers. But at the time, if you had a really good day 5 blastocyst and you were under age 35, we would steer people towards just one embryo transfer. And over time, we've started to apply eSET to more patients, especially the ones who are over 35 and have done genetic testing on their embryos, that comprehensive chromosomal screening. Then we recommend that they only transfer one at a time as well. Comprehensive chromosomal testing has not been proven to improve the chance of pregnancy or decrease miscarriage rates, but most of us feel that eventually it will be. So right now if you have normal blastocysts, even if we don't know if they have a minor gene deletion or they could be really bad, or a cytoplasmic problem like really bad mitochondria, if they have 23 pairs of normal chromosomes and it's a good blastocyst from day 5, you should probably only transfer one.

Q: Do patients who undergo IVF hear about eSET beforehand, or do you tell them about it?

A: I think most of them have done reading about it. I would say about 60-70%. The other ones, a lot of the time will not know anything about it and will be much more likely to ask you to do a 2-embryo transfer to just improve the chance of pregnancy. But there's the little chart we can pull out from CDC that goes through some of the troubles with twins, and that you're actually more likely to have a healthy baby that's not affected if you just transfer one at a time.

Q: I was going to ask if you had something like this to give out to patients.

A: When you think twins, twins get delivered at about 35 weeks, 3 days, instead of 39-40 weeks. So most of the neural development happens in the last few weeks of pregnancy. So we think twins never really reach their full potential.

Q: Are there certain circumstances where you wouldn't recommend eSET?

A: Now if they're over 35 and they haven't tested the embryos, if they're day 6 blastocysts, in that situation it's reasonable to transfer 2. If you do single embryo transfers and don't get pregnant, most of the patients will come back and almost demand that you do a 2-embryo transfer. Over age 40, you're better off transferring 2. If you go to 3, or 5, I think that's a little iffy, but definitely over 40 I would transfer 2.

Q: If you recommend to eSET to patients, do most of them usually follow your recommendation?

A: Yes, they do. The great thing is that with the Internet, they can go home and look it up themselves. 20 years ago when you tell people stuff, a lot of the time they wouldn't believe you. Now they can go home and independently confirm what you're telling them. So when you ask them if they know what cerebral palsy is, and they say they do, you can tell them that it's 4-6 times more likely if you have twins. It makes you think a little bit. The other thing that we'll do a lot of the times is that if it's a money issue, we'll tell people that if they let us do one single-

embryo transfer and they don't get pregnant, we won't charge them for the next one. To split them up.

Q: If you have patients that are good candidates, and you've told them about eSET, are there other reasons they might refuse?

A: Some still have it in their minds that twins are cute. A lot of patients from Mexico have friends that have had twins with some sort of fertility treatment, so they tend to think of it not as a bad thing. A lot of the Mexican patients have a vast majority of them delivering by C-section now. C-section is seen as a standard thing, so when we tell them that if they have twins, they're more likely to have a C-section, that's fine. They don't think that's bad. We really bring the hammer down and say that they should not do 2-embryo transfers, and it's pretty rare that people say no and still want to do it. In Mexico they do C-sections routinely, and part of it is the scheduling. They like to schedule rather than having to be all night laboring. There's also a perception among patients that you don't have to be bedraggled by having to labor for 12 hours. That you can show up and know exactly when you're going to have the baby. Also, a lot of them are worried about pelvic floor problems. They're worried about pelvic floor injuries from vaginal deliveries. Certainly as patients have gotten more obese and less fit, they're more likely to get pelvic floor damage.

Q: For patients that do eSET, have there been patients that have gotten natural twins from one embryo?

A: I always tell them that the chance of having twins is about 1-1.5%. Those are identicals, so that's an embryo that has split. Unless they happen to have ovulated and have intercourse along the way, so there's an egg coming from above and we're putting in an embryo from below. But most of them are going to be identicals, so then you get into the much more morbid pregnancies, where you could have two kids in the same sacs. And then the cords could get entangled, or they could start getting twin-to-twin transfusion syndrome. So those are more complicated pregnancies if that happens. We've had one person who did 1-embryo transfers twice, and each time she had a split.

Q: According to the CDC, using eSET has a success rate of about 21%, which seems pretty low. It's from 2013, so it might have changed since then.

A: I think the rate is more around 40-50% here, depending on the age of the patient and indication. The older you get the worse it's going to be. Still, it's probably better to split up those embryo transfers rather than doing 2 or 3 at a time. I found this paper that showed that the more embryos you put in, the chances weren't just linearly, they went up more than that. So the embryos actually help themselves implant, so they're creating their own environment and nutrient media that helps with implantation. It's always been very tempting to do more than one embryo transfer, but it's complicated.

Q: When you tell patients about multiple gestation, is there anything else besides what's on this sheet that you say about it?

A: The stuff that's not there is that the divorce rates are a lot higher for twins. The toll on the woman is pretty brutal. The person who can survive without having some significant abdominal wall connective tissue problems after a twin pregnancy, abdominal wall hernias, huge numbers of stretch marks, big varicose veins of the vulva, all these other things. That's just really, really common. What I think is interesting is that of the patients who had twins with IVF and come back here to have a third baby, nobody in the last 5 years has let me do a 2-embryo transfer. Because they're rough. It seems like it's 'two for the price of one' or 'then we can get it all done at one time', but it's not really true. Twins are really rough. Having two screaming babies who wake each other up at night is really rough. It's almost like you need a third person doing childcare to help out, otherwise nobody gets any sleep.

Q: Do you do pre-implantation genetic screening?

A: Yes.

Q: Does that encourage patients to do eSET more?

A: Yes, it really does. They get to choose. The ones that want a certain gender get to choose a certain gender.

Q: Besides the paper, are there websites that you might have patients look up about eSET?

A: Yes. It just depends on what an individual practice is doing and what their pregnancy rates are for single embryo transfers. If you're hitting in that range where you're at 35-40% at least for single embryo transfers, most patients will go with that. If you're doing better, like we were for the year up to the day, the chance of getting pregnant with mostly single embryo transfers was 63%, and after you filter out miscarriages, the ongoing were still over 50%. If a patient thinks that if they do get pregnant, they won't have all these other nightmare problems, then they're much more likely to go ahead with eSET.

Q: For patients where eSET doesn't work the first time, you said some of them ask for two embryos the next time. How does that compare to just using eSET again?

A: If they're really young, under age 35, and they have a bunch of good day 5 blastocysts, I will ask them to let me do just another one, and if they don't get pregnant, we'll do the other ones free. That's actually what a lot of places in Europe have done, to try and move people. Places in Europe tell patients that they can do single embryo transfers all year long, we'll pay for them. If they do a 2-embryo transfer though, we won't pay for it. A thousand or two thousand dollars is enough a disincentive that most people will actually do single transfers.

Q: Do most other clinics also offer eSET?

A: They'll offer it, but even if some data disagrees with it, most practices have noticed that if you do 2-embryo transfers, you get a better pregnancy rate. We've certainly noticed that too. I know that if I have somebody who's under 35 and I put in two, I'm probably going to get rates of 70%

or more. It's not going to be 100%, but it's going to be better, but then you have chances of twins. And twins are more likely to miscarry, more likely to be damaged or have cerebral palsy, or learning disabilities. In our field, I wish the government would regulate it or at least be more aggressive, like in Europe where they say you can do a 2-embryo transfer, but the patient has to pay. It would level the playing field, because I feel like there are ethical practitioners, and then there are practitioners who are chasing the higher pregnancy rates because they know when people go to the SART website, the first thing they look for is clinical pregnancy rates. They have a big header that says not to use this to compare pregnancy rates between clinics, but they all do. And even the bigger practices now cherry-pick patients so that they only put the most favorable prognoses patients into the group they're reporting to SART, and put the rest of the patients into study groups. So they don't turn those patients away, since they want their revenue, but on the other hand, they're not including those patients in the data they send to SART. Some of these practices are doing 4000-5000 retrievals a year, and they're doing 13-15 a day, but they're only reporting 900 women over 35. It's not a level playing field, it's a competitive market since people are paying out of pocket primarily still in this country, and they don't understand about the twin thing and want to get pregnant.

Q: So if there was more regulation like in Europe, do you think we'd see better rates?

A: We'd see better outcomes across the board. We'd see far fewer twins, far fewer preterm babies. But there's competing interests. Back in 1999 the university has this self-insured model where the university was paying for the insurance for the employees. The prior reproductive endocrinologist down there was a multiple-transfer guy, so he created a lot of twins and triplets.

When I came down there, the administration approached me and said they would like to stop this and lower the costs on this because the NICU babies were costing a fortune. They cost at least a couple of grand a day, and some were in there for months at a time. We went over the ASRM guidelines for transferring embryos. Although if you're decreasing healthcare costs for the system, you're taking patients away from the NICU doctors.

Q: Do you talk about eSET on your website? Do you know if other clinics offer pamphlets or papers on eSET?

A: I don't know if we do or not. I don't know about other practices, they might be much more aggressive, so I don't know if they would promote single embryo transfers.

Q: Thank you so much for talking to me today.

A: You're very welcome, feel free to call or come back if you have any further questions.

Interview 2

Q: Do patients who undergo IVF know what eSET is beforehand? Do they do research beforehand before they come to you?

A: They will have some idea, some don't. Some are more educated and they do more research before they come, and sometimes they don't, so it depends. But when we do speak to them about

the transfer, we do explain to them. And we also explain to them that we have guidelines that we have to follow. We have guidelines by ASRM, the American Society for Reproductive Medicine, that set a guideline for different age groups, how many embryos that we have to transfer. Under less than 35 and if their diagnosis is good, and the probability of getting pregnant is good, then we have to recommend transferring one embryo. The patient chooses, at that point, whether they want to transfer one or two embryos.

Q: How often do you recommend eSET to patients?

A: We do present to them single embryo transfer with all patients. We do talk to them about that, but we always try to follow the ASRM guidelines. So if they're older, we will say that there is single embryo transfer, but this is what we recommend. This is the way that you will have higher chances of getting pregnant.

Q: What are the circumstances where you wouldn't recommend eSET?

A: If they are less than 35 years old and have tried multiple times with IVF and embryo transfer and did not get pregnant, then we wouldn't recommend that they transfer more than 1 embryo.

Q: Once you recommend eSET to your patients that have good chances, do they usually follow your recommendation?

A: A lot of times they don't. We make a recommendation because we look at the embryo quality. We make a suggestion to the physician at the time of transfer of how many embryos they should transfer. If we know that an embryo looks really good and has the highest potential, and they're less than 35, then we'll recommend transferring one. Then the physician will use that as a guideline to talk to the patient just before the transfer, saying that the lab recommends one transfer because the quality is very good. At that point, the patient will decide if they want 1 or 2. There's a struggle where one partner wants to have 1 embryo transferred and not have multiples, and the other partner wants to have multiples. So there needs to be a discussion. We try to give them all of our data so they can get well-rounded information before they make a decision.

Q: That's one reason why patients would refuse eSET. Are there other reasons why patients might refuse eSET?

A: Just financial reasons and emotional reasons. Or if their friends have twins, then they might want them. We've had patients that adamantly demand transferring two because their friends have twins.

Q: Do people refuse because they deliberately want twins, or multiples?

A: Yeah. And triplets, we really don't want that and try to discourage it. Sometimes the clinician will say no, because the risk is too much higher. And patients understand that.

Q: Does your clinic offer any incentives for doing eSET?

A: It's really hard to give incentives to one patient and not to others. We try to have everything be standardized, because it's a small community and patients do talk. If they find out we do one thing to one patient and not to others, they won't be happy.

Q: Do you think patients who refuse eSET might have a lack of awareness about the risks of multiple gestation?

A: Most people don't know. They romanticize having twins or multiples because they see others having them. You see movies about having twins and how that would be so much fun. They don't think about the health risks. So the clinician's job is to discuss the health risks. Also the patient has health risks too. She may have to be bedridden at 18 weeks of pregnancy up to 36 weeks. If she's working, she may not be able to work, which is a big financial burden. They could have a higher miscarriage rate, complications with the fetuses. We present all that information to patients, and they have to sit and think about it.

Q: What do you normally tell patients about the possibilities of multiple gestation?

A: The physician talks about preeclampsia, high blood pressure, being bedridden and unable to work, premature birth. Babies who are born premature have to remain in the hospital longer, and the mother has to go home, so she has to go back and forth.

Q: Does your clinic do pre-implantation genetic screening? Do you think that affects eSET rates in your clinic?

A: We do. The statistics show that if you transfer one normal embryo, the chance of pregnancy is higher and the miscarriage rate is less. We do encourage them to do PGS. It is expensive, and that's another thing where patients don't have the money or financial means to come up with another \$5000. So they have to take a chance.

Q: For patients who have to make difficult financial decisions, do you think sometimes they refuse eSET because they want to get as many chances as they can get in one cycle?

A: Yes, they want the highest chances possible of having a baby.

Q: Do you think rates of eSET would be different in countries that have universal healthcare systems?

A: I think Italy has single embryo transfers and Spain, they have socialized medicine. So they do have higher rates of single embryo transfer. They're more regulated than America. The pregnancy rate is a little bit lower since it's a single embryo transfer. Here in the U.S., some of the clinics, depending on how the clinician feels, have mandatory criteria. We will not transfer more than one embryo if you meet that certain criteria from the ASRM guidelines. They don't want to, no matter how the statistics may look, take the risk on patients or babies.

Q: Part of this study is seeing what I can do to help increase patient knowledge about eSET, such as pamphlets or posters. Do you offer any pamphlets to patients with that information?

A: No, we don't. And I don't think any of the clinics offer that. I haven't heard of that.

Q: Would you be open to that idea?

A: Yeah, I don't think we've really thought about it. A lot of the IVF clinics coordinate with patients and try to educate them as much as they can. RNs and practitioners try to educate them. Having them go through the Internet and looking up risks. But we don't have a pamphlet. I think the topic is brought up with every patient, even with older patients. We always prefer transferring one, but depending on age criteria or embryo quality in older patients, we really do recommend transferring two embryos, or three, if it doesn't look good.

Q: When you talk to patients about eSET, do you recommend any specific resources to them?

A: We usually refer them to the ASRM. ASRM has a patient information website that has really good information for patients. We prefer to do that because ASRM is the one that sets the guidelines and makes the rules. They don't sugarcoat anything and just give the facts. We want patients to see the facts and make their own decisions based on those facts. They come with this fantasy idea and then get information. ASRM has a lot of information on their website, like patient guidelines and risks.

Q: Thank you so much for the interview.

A: You're welcome, and good luck.

Interview 3

Q: Does your clinic offer eSET as an option?

A: Yes.

Q: When did you begin offering eSET?

A: I think we've always offered it.

Q: How do you think the usage of eSET in your clinic has changed over time?

A: I don't think it's changed very dramatically. Very few people choose it.

Q: Do patients who undergo IVF often know what eSET is beforehand?

A: Yeah, I think so.

Q: Do you know where they might find out about it beforehand if they research it on their own?

A: Maybe the Internet.

Q: How many patients do you think only hear about it through clinical recommendation?

A: Well, we always discuss the probability of pregnancy and the number of embryos transferred, and the pros and cons we always discuss with all of our patients. I think all of our patients are very well-informed about what the natural pregnancy rate is, what the pregnancy rate is based on their age and their problem, and then they make an informed decision about how many embryos to transfer. And very few people choose to transfer one.

Q: How often do you recommend eSET to patients undergoing IVF?

A: I always offer it as an option.

Q: Are there patients that bring it up as an option on their own?

A: In the past year no one has mentioned it to me.

Q: Approximately what percentage of your patients go through with eSET?

A: Very little. I'd say less than 5%. Maybe even less than that.

Q: Are there certain circumstances where you wouldn't recommend eSET to a patient?

A: Absolutely. Older patients, because they have a harder time getting pregnant.

Q: After recommending eSET to patients, do they usually follow your recommendation?

A: I would say yes, patients usually follow my recommendation specifically for eSET.

Q: Does your clinic offer any incentives for using eSET?

A: No.

Q: If patients refuse eSET, do you know of their reasons or do they give any reasons for doing so?

A: Because they're very interested in achieving pregnancy in that cycle. They want to increase their pregnancy chance.

Q: Are there any more common reasons? Such as wanting twins?

A: Occasionally patients say they actually want twins or say they would be more comfortable with twins.

Q: Do you think that patients might have a lack of awareness about the risks of multiple gestation that might contribute to low rates of eSET?

A: No, I think all of our patients are very aware of the risks of multiple pregnancy, giving their clinical circumstances and given their age. I think they're very well-informed about that. On the other hand, patients are very interested in getting pregnant, so it's a balance between the risks of multiple pregnancy with the chance of getting pregnant.

Q: What do you normally tell patients about the possibility of multiple gestation?

A: Well, I try to inform them as best as possible based on the best possible data for their particular risks of multiple pregnancy. It's very individual for individual patients. It depends on their age, their problem, if they've had children before. There are many factors that determine how we calculate their risks for multiple gestation. We also talk about the natural rate of twinning. Twins happen naturally in humans, as do triplets, but triplets are very, very rare. Twins are not particularly rare. We always try to make a realistic expectation about the baseline risk of twinning. The baseline risk of twinning is not 0, people get pregnant and they have twins sometimes. And the risk of having live-born human twins is 1 in 67. It's not rare. So we're comparing our rate of twinning to the natural rate. Most fertility treatments have a higher rate of twinning than nature. We certainly would like to prevent all higher orders births, so we don't want people to have more than twins ever. But I think that most patients accept the fact that sometimes twins happen. I think many patients are comfortable with that. I've had some patients

who've had two sets of twins, but that's a different story. But again, I think most patients are very aware of the risk of twins given the fertility treatment that they're undergoing. And that's including patients that are not doing in vitro. Patients have all kinds of treatments for getting pregnant, and in vitro is just one of them.

Q: Does your clinic do pre-implantation genetic screening?

A: Yes.

Q: How do you think that might affect eSET rates?

A: In theory, that would increase the chance of pregnancy, because we know that we're transferring a healthy embryo, and the chance of having a miscarriage due to aneuploidy or errors that we've detected with a screening is decreased. But it's not 100%, we don't have 100% pregnancy rate. So a lot of patients come in and think that we'll just screen the embryo and that should give a 100% pregnancy, but that's not true clinically or biologically. There are other reasons why embryos don't implant, and there are other reasons why embryos miscarry. So pre-implantation genetic screening is a great tool, but I think it's being overused and it's being touted too exuberantly as a way to increase the pregnancy rate of single embryo transfer. If it was true, everyone would get pregnant. Biology is difficult, and screening is very good nowadays. But the problem with screening is that there are false positives and false negatives as well, and the cost of the screening, and the overall effect on the chance for pregnancy. Everyone is working

towards being able to pick out the perfect embryo to give a 100% pregnancy rate, that would be ideal. But it is an ideal, not a clinical reality, and therein lies the problem.

Q: If you recommend eSET to patients, do you have any resources that you direct them to, or pamphlets?

A: No. I'm sure there are lots of resources though, such as online.

Q: Do you think you would be interested in a pamphlet that informs patient about eSET?

A: No, and the reason why I say that is a difficult thing. I think pamphlets have a role when you're trying to educate people about public health issues that are potentially able to reach the masses. For example, I think having pamphlets for taking folic acid prior to pregnancy in preparation would be very useful, because that's a very useful public health concern that we could disseminate to a lot of people to get the word out. Or pamphlets for immunizations, for example. And HPV is a classic example where the word is not out about how important that is, and people still have negative connotations about that. So those types of things that are good for the public in general, where a lot of people get the message and we can put it in simple layman's terms, and then produce a pamphlet that we could give to people, instead of spending a lot of time trying tell them individually. One example is syphilis, which should be eradicated but it isn't. I see big posters on the bus stop signs trying to educate people about the dangers of syphilis, the diagnosis, and getting treatment rapidly. Those types of things I think are great for pamphlets. eSET doesn't fall into that category. It's very specialized, and it's not something you

want to educate the entire public on. Most people don't need it, and the people that come in for in vitro are getting very intensively counseled about what we need to do to help them get pregnant, and what their chances for pregnancy are. Their circumstances are very individualized. I think there's good basis for having programs to educate large portions of society that would benefit from learning about things like folic acid. Women who are trying to get pregnant should know that they should take folic acid, and that's why we supplement food for young women just in case they accidentally get pregnant. We're trying to improve the overall health in the community and society in general. I think the issue of eSET doesn't fall into that category.

Q: Thank you so much for the interview.

A: It was very nice to see you.

RESULTS

According to the transcript, the clinics that were interviewed all offered eSET, although usage varied in all 3. One clinic noticed that their usage of eSET has been increasing over time with a current rate of about 40-50% of patients, another clinic stated that patients often don't go with eSET, and another clinic stated that only around 5% of their patients decide to use eSET. The clinics also recommend eSET as an option to patients, but who they offer it to depends on different qualifications. The clinics generally follow the guidelines put forth by the American Society for Reproductive Medicine (ASRM), which recommends patients who are 35 years or younger with good embryo quality ("Single Embryo Transfer", n.d.). One clinic has begun to

extend recommendations to patients over 35 who have done PGS to ensure high-quality embryos, and another clinic brings it up as an option with all patients, but not necessarily as a recommendation. The clinics also agreed that they wouldn't recommend eSET to patients that definitely do not qualify under the ASRM guidelines, especially older patients over 35 with unknown embryo quality, or patients under 35 who have tried IVF multiple times without success.

Regarding patient awareness, the level of patient education seen by the clinics also varied. Some clinics said that many patients have heard of eSET, while another clinic said only some of them know what it is. One clinic also stated that although their patients may know about it, eSET is rarely brought up by the patients themselves as an option. All the clinics say they educate patients about eSET prior to the patients making any decisions.

When clinics do recommend eSET, whether patients follow their recommendations also seems to depend on the clinic. Two clinics stated that patients do follow their recommendation, while another clinic stated that patients often don't. Several of the reasons that clinics surmised why patients may refuse eSET included having financial issues, wanting twins, or wanting to increase their chances of pregnancy. Regarding the financial issues, one clinic said that they offer a second eSET cycle free if the first one does not result in pregnancy. However, the other two clinics do not offer any specific monetary incentives for doing eSET, with one clinic stating as a reason that it's hard to create a standard for patients whose circumstances are highly variable.

Patient awareness about multiple gestation was another topic discussed in the interviews. One clinic said that their patients were usually well-informed about the risks, but are also very interested in getting pregnant. Another clinic stated that most of their patients don't initially think about the risks, especially those who want twins or multiples. All clinics stated that they

talk with their patients about the risks of multiple gestation, and that patients will make a decision with all of the information they have. Clinics tell patients about risks such as preeclampsia, premature birth, longer hospital stays, abdominal tissue problems, and even divorce. One clinic did offer an information sheet regarding eSET and the risks of multiple gestation. Other clinics did not have any such information, although one clinic stated that they often refer patients to the ASRM website, which has patient resources regarding multiple gestation (“Multiple Births or Multiple Gestation”, n.d.).

Clinics were also asked about PGS in conjunction with eSET. All of the clinics offered PGS as an option during fertility treatments. Some clinics said that PGS does help encourage patients to use eSET because it increases the chance of pregnancy and decreases the rate of miscarriage, and allows patients to choose a certain gender. Another clinic said that PGS should increase chances of pregnancy, but that it’s not 100% due to other various reasons why miscarriages may happen. The clinics did remark on the cost of PGS being potential problems as well.

When asked about a potential pamphlet or poster that could inform patients about eSET, the clinics had a variety of responses. One clinic stated that while they do provide an information sheet about eSET, they do not talk about eSET on their website, and doubt that other clinics offered specific information regarding eSET. Another clinic stated that while they refer patients to the ASRM, they don’t have any handouts of their own regarding eSET, but may be open to having one in order to educate patients as much as they can. Another clinic stated that a pamphlet or poster for the general public is probably not the best fit for eSET, since it’s a very specialized health issue.

DISCUSSION

Although only interviewing 3 clinics doesn't provide a comprehensive outlook on the usage of eSET in fertility clinics, it does provide some insight into several issues, such as how much patients know about eSET, reasons why patients may not choose eSET, physician variations with respect to their individual philosophies, and possible methods for increasing eSET usage in clinics. The clinics that were interviewed all offered eSET, but that may not be the same of clinics across the U.S. Patient awareness often starts with clinical awareness, so whether a clinic is aware of eSET and is willing to offer it as an option can make a huge difference in eSET rates.

It then appears to vary with clinics whether patients have knowledge of eSET or multiple gestation. Whether patients research the topics before coming into fertility clinics is up to the patients themselves, but the clinics all seem to be consistent in providing patients with information prior to any fertility treatments. However, despite clinical recommendations, there are patients who are good candidates for eSET that do refuse the procedure. From the interviews, it appears that the more common reasons are that patients don't think eSET will be as successful as transferring multiple embryos, patients face financial issues that encourage them to achieve pregnancy within the fewest possible cycles, and patients deliberately want twins or multiples.

The pregnancy rate of eSET is a highly variable subject. As mentioned before, several studies involving eSET offer conflicting information about pregnancy rates, making it hard to determine whether eSET really does have a lower pregnancy rate or not. There are also other variables to consider, such as the quality of embryos being transferred. PGS can be used to examine the embryos for the one with the highest quality available for transfer. If eSET is accompanied by PGS, that should improve the rate of successful pregnancy with eSET without

having to implant multiple embryos. Another factor is the qualifications for patients to be good candidates for eSET. The more patients that follow the guidelines proposed by ASRM, the better the chances of pregnancy should be.

The results from previous studies also depends on how the information was gathered. Studies may have chosen a population that included patients outside of the ASRM guidelines who did eSET regardless, which would lower the resulting pregnancy rate. The study by Stillman (2009) did use a set of criteria for patients that resembled the ASRM guidelines; however, the research done by Adamson (2015) did not specify the demographics of the patients, and the study by Gerris and Sutter (2009) examined trials that involved both randomized selection of patients and patients who had good transfer prognosis. If the studies involve multiple clinics, then the pregnancy rates may be an average across the clinics, and don't truly represent individual clinic results. For example, one clinic that was interviewed stated that about 40-50% of their patients chose eSET, while another clinic stated that only 5% of their patients chose eSET. An average would result in an eSET rate of 25% across both clinics, but it doesn't accurately reflect the differences between clinics, such as whether one clinic promotes eSET more than the other. If this process was applied to determining pregnancy rates for eSET, similar misconceptions could be made about successful eSET.

According to the clinics that were interviewed, eSET seems to have lower rates compared to other methods of transfer, such as DET. One clinic stated that their pregnancy rate for eSET was around 50%, but that they also noticed doing DET usually results in a higher pregnancy rate. Another clinic agreed that eSET has a lower pregnancy rate, while another clinic stated that they don't have the opportunity to use eSET that often, so it's hard to determine. These clinics don't represent all of the fertility clinics in the U.S., so further comprehensive research may lie in

surveying fertility clinics across the country about whether they offer eSET as an option and what their pregnancy rates for eSET are.

Another issue patients have with eSET is the financial concerns that accompany eSET. With the potentially lower pregnancy rates, patients may not want to use eSET because they lack the financial means to pay for multiple cycles, should eSET not work the first time. One IVF cycle costs on average \$12,000, with a range of \$8,000-\$15,000 depending on the clinic (Sherbahn, n.d.). In addition, medication for ovarian stimulation costs around an extra \$3,000-4,000 (Sherbahn, n.d.). PGS may be used to help increase the chances that eSET is successful, but is another additional average of \$3,500 (Sherbahn, n.d.). If an IVF cycle isn't successful the first time, not only would the patient have to pay for another IVF cycle, but they may also have to wait another couple of months for egg retrieval for fresh embryo transfers. For some patients, it seems more ideal to transfer multiple embryos at once to guarantee pregnancy, even if it results in twins, than to go through the timely costs of multiple cycles. As mentioned before, many insurance plans in the U.S. do not cover IVF treatments. ART is only covered in 15 states in the U.S., which puts more pressure on patients to ensure their treatment is successful once (Tobias, Sharara, Franasiak, Heiser, & Pinckney-Clark, 2016).

There are ways to compensate for financial issues. Some fertility clinics may offer financial plans if a patient chooses to use eSET. One clinic that was interviewed offers patients a free additional IVF cycle with eSET if eSET isn't successful the first time. Another clinic mentioned how some fertility clinics in Europe will pay for eSET but not DET. The study by Stillman, Richter, Banks, and Graham included a program that offered six full cycles of IVF for just the initial fee of one cycle, which resulted in patients choosing eSET at higher rates (Stillman et al., 2009). A study by Tamara Tobias (2016) found that providing patients with

financial incentives caused a majority of patients to choose eSET. Several countries have programs that reimburse the costs of ART, and have seen an increase in eSET cycles and a decrease in multiple births (Tobias et al., 2016). However, there are also many clinics that do not offer any beneficial monetary incentives for using eSET, as is the case with two of the clinics that were interviewed. Patients may be recommended to research different fertility clinics for IVF costs and potential financial plans involving eSET and/or PGS.

The interviews also suggest that patients often want twins deliberately, or are not opposed to the idea of having twins. All of the clinics stated that they have had patients who intentionally want twins. One clinic said that patients who have friends with twins often desire twins as well. This brings up the issue of whether patients fully understand the risks of multiple gestation and want twins in spite of that knowledge. According to the interviews, patients are either already aware of the risks, or are informed by the clinics of the risks. One clinic said that patients often follow their recommendation of eSET, while another clinic stated that patients often don't.

Thus, there are patients who do change their minds after patient education, but there are also those that still want twins after learning about the health risks of multiple gestation. It may be that some patients have a lack of own experience that would deter them from trying for multiples. According to one clinic that was interviewed, patients who previously had twins through IVF and returned to the clinic for another baby never asked for DET afterwards because they realized how rough it is. For patients who have never had twins before, it may be hard to imagine some of the difficulties that accompany multiples, including not only pregnancy complications but also lifestyle accommodations. Presenting a pamphlet to patients that outlines the risks of multiple gestation, but also provides first-hand accounts from patients who have had twins.

A pamphlet discussing the risks of multiple gestation, the benefits of eSET, and experiences previous patients have had with eSET or DET may be a widespread way to educate patients about their possibilities with fertility treatments. According to the interviews, it appears that most clinics do not have specific pamphlets for patients to read about eSET. One that targets good candidates for eSET would also be more specialized, since not all patients are recommended for eSET. Patient education through the provision of materials has been stated to have a significant impact on patients, who start to prefer eSET over DET (Tobias et al., 2016). With access to educational materials combined with counseling from fertility clinics and self-research, patients may begin to increasingly choose eSET as their preferred method of embryo transfer, potentially increasing the use of eSET in fertility clinics.

Further research may involve the previously suggested surveys of fertility clinics about their rates of eSET and their pregnancy rates with eSET, which would help understand how widespread eSET usage is in the U.S., and whether it is as effective as DET or not. A survey of patients would also provide more information about their awareness of eSET and reasons for choosing or not choosing to use eSET. Investigating different financial options in fertility clinics and seeing whether clinics would be interested in offering financial incentives regarding eSET and PGS would help encourage patients to choose eSET as well. There is also the possibility of more patient education beyond pamphlets, such as videos, although pamphlets have the advantage of being highly distributable and requiring less commitment to read.

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