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Single and Dual Embryo Transfer, How Far We Are?

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Abstract Since decades back, specifically since the development of infertility treatment was progressively advancing, the multiple pregnancy is increasing drastically and of the major contributors to this increment is assisted reproductive technology ART, which reflects an increased risk for both mother and fetus other than being a health hazard. We reviewed the literature systematically to explore and compare the dual embryo transfer DET with single embryo transfer SET weather electively or not in more viewpoints like financially, and scientifically and finding out which of these policies may give better outcome by analyzing both in a neutral broad spectrum manner. Our results were given upon some clinical trials, and in part upon other articles found in the literature, but the comparison between all these articles found to be unreliable due to the huge variation between them all, ending up finally that SET has the advantage of minimizing the twinning and multiple pregnancy rate MPR. On the other hand SET has less benefit when compared to DET in the matter of implantation rate IR, ongoing pregnancy rate OPR, but a comparable results may be obtained when applying elective single embryo transfer eSET of frozen-thawed embryo. We concluded that larger clinical trials should still be encouraged for such comparison especially in applying same criteria for both methods.

Keywords: *assisted reproductive technology, twins, single embryo transfer, and double embryo transfer*

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1. Introduction

During the last three decades, the treatment of infertility has been an area of wide conflict, and multiple techniques are being applied, taking in consideration the major role ART is playing in the increment of multiple pregnancy rate which is considered as a health hazard .To optimize the modality of certain service offered in the best manner, numerous articles and opinions were published in the same regard but in many fashions. Accordingly, this review was done to contribute in the debate of standardizing the optimum methodology. Aiming for giving the desired results according to what is known as best technique, whether by SET, eSET or DET in ART which illustrates the importance to various aspects as well, as patient counseling in a neutral way after explaining the pros and cons objectively.

The art of ART is no more a new trend, it became a well established mature science, and usually such techniques are evaluated upon outcomes after assuring the safety of it. When evaluating the effectiveness and success outcome of the ART, we find that multiple pregnancy is considered as a less favorable outcome, risk, or even a complication of the procedure performed due to the impact of the multiple pregnancy on both maternal and fetal point of view. Apart from this all, the pregnancy itself will be jeopardized upon the quality of it, other than the medical, financial, psychological, emotional, and social sequel of multiple pregnancies. Moreover, such importance stands out especially knowing that the children born after ART constitutes 1-3% of the overall number of live births in European countries [1], and of these, about 20-30% are twins, whereas only 1% are twins following the spontaneous conception pregnancies according to Centers for Disease Control and Prevention [2].

Awareness is growing that the preferred endpoint of fertility treatment should shift towards healthy, term, singleton births rather than merely pregnancy rates [3,4,5,6]. For that reason, many health care givers are trying to adopt the idea of eSET followed by one or several frozen-thawed embryo transfer FET cycles which has been shown to reduce the incidence of multiple pregnancies and maintain acceptable live birth rates. In many randomized controlled trials [7-12] and retrospective studies [13-18], recommendations were that all efforts should be considered to avoid such iatrogenic complication. Fortunately, compliance of fertility treatment could be achieved by applying the eSET.

However, taking into IVF physicians account such treatment option as a first line or golden standard rule unless other circumstances may necessitate the SET or DET, would enormously contribute in better treatment results. In this systematic review we analyze studies done, concluding that ART success rates would certainly be improved by applying the aforementioned modality especially when we know that one of the main reasons of the multiple pregnancy increment lately is treatment of infertility and embryo transfer policies.

2. Materials and Methods

2.1. Inclusion/Exclusion Criteria

The review personnel are of interest related profession who performed a computerized comprehensive search without pertaining restrictions. Searching was done in the PubMed and the Cochrane Central Register of Controlled Trials (Central); it was conducted to identify full publications of relevant studies published about SET in comparison with DET. ART glossary was used for terminology such as Assisted reproductive technology ART, twins, single embryo transfer SET, and double embryo transfer DET.

Search steps are illustrated in [Figure 1], finding 62 articles of which 49 were identified as being from specialized web sites and ended up finally by analyzing 4 RCTs extensively. The beginning of search consisted of randomized and non randomized clinical trials, reviews, comments, analysis, debates, and reference lists. Additionally, various papers and presentations during congresses, articles and comments written in certain journals, and ideas exchange with some researchers, authors, co-authors and specialists interested in the same domain were included. These all were systematically filtered many times as some of them were excluded for being only abstracts, unrelated directly to the main topic or as they were in languages other than English or duplicated. The search included researches published related to the main topic of comparison between SET and DET. Non specialized web sites articles, observational studies, reviews, and limited access RCTs were excluded. Data from all the previously mentioned studies and their reference lists were collected and complete comparison of pregnancy rate, pregnancy birth, and live birth rate was done.

2.2. Multiple Pregnancy Overview

Multiple pregnancy rates are variable from a country to another, being affected by many factors like region, age, parity, race and the usage of ART or infertility treatment but the monozygous twins MZ incidence is almost the same all over the world being about 3.5 per 1000 births [19].

In comparison with singleton pregnancy, twins and multiple pregnancy has far more risks being maternal or fetal knowing that some of these risks might affect mothers and babies in the same time [Table 1]. Away from that, there are the social factors which affect the couple and their relatives from the direct or indirect sequences to this matter and that could be reflected upon quality of life as well.

The financial factor should be addressed, as it affects the atmosphere which might in a way or another affect the pregnancy per se or the quality of services that should be offered to the multiple pregnancy mothers, these are like more frequent prenatal visits which might be necessary for the detection in an earlier time of any pathology could exist, needs for more frequent hospital admissions in cases of multiple pregnancy situation is well acknowledged by specialists.

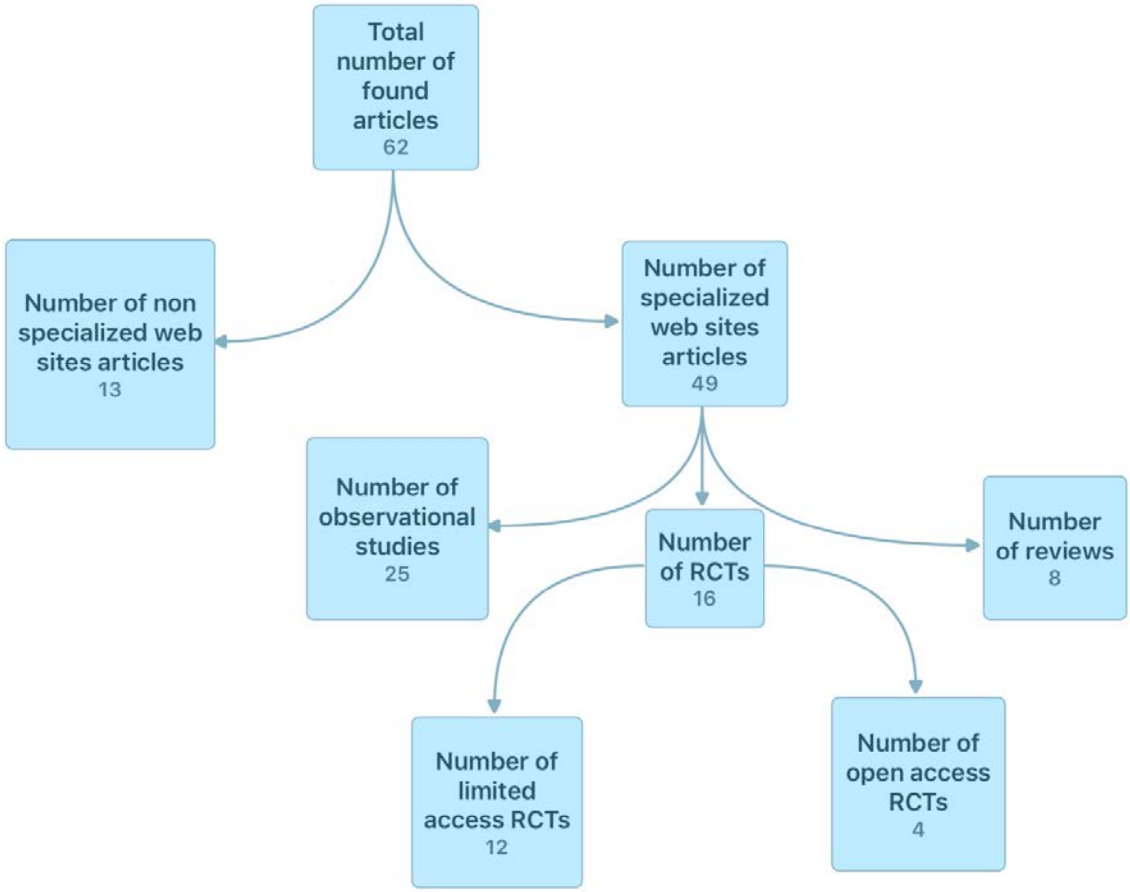

Figure 1. Systematic review flow chart illustrating search steps and strategies for SET DET comparison

All these risks are increased when ovulation induction or infertility treatment medications are given and they correlate directly with the number of embryos transferred. Consequently, the best way to decrease the incidence of multiple pregnancy is by reducing the number of transferred embryo (preferably to one), after a proper counseling for the couples.

2.3. Twinning after ART

It is progressively more recognized that ART increases the incidence of monozygous MZ twinning 2-6 fold, particularly two blastocyst transfer [20], although the majority of twins following ART cycles are dizygotic twins (DZ). Apart from this, multiple pregnancy is considered the most common complication of ART. ESHRE report in 2004 stated that compared with earlier years, the reported number of ART cycles in Europe increased and the pregnancy rates increased marginally, even though fewer embryos were transferred and the multiple delivery rates were reduced [21,22], after knowing that approximately 25% of pregnancies achieved following IVF techniques when two or three embryos transferred are twins, consequently, we understand how important is prioritizing the avoidance of twinning through the ART treatment at least by transferring one embryo freshly and if other embryos are available, they can be frozen, and the patient is free to undergo repeated SET until she achieves the desired goal, or until all embryos are consumed.

The protocol of transferring one embryo whether selectively or when only one embryo is found is already applied in many Scandinavian countries especially if the patient is 35 years old or less, and the results of the applied protocol are satisfactory.

2.4. Chorionicity and Zygocity

In multiple pregnancies, chorionicity plays the leading role of defining how far the maternal and perinatal risk is. All DZ twins are dichorionic DC. Perinatal mortality is 2-3 times higher in monochorionic MC compared to DC twins [23,24]. And the related morbidity and mortality is attributed to the placental vascular anastomosis which affects the circulation in MC twins.

Table 1. Maternal, Fetal, and combined risks found in twins/multiple pregnancies in comparison to singleton pregnancies

Maternal risks	Fetal risks	Combined risks
More disturbing early pregnancy symptoms. Abortion. Preterm delivery. Anemia. Hypertension. Ante- and postpartum hemorrhage. Hydramnios. Operative delivery. Postnatal problems.	One of babies' sudden death. Vanishing twin syndrome. Neonatal death. Stillbirth. Intrauterine growth restriction. Congenital anomalies in one or both of the twins. Twin reversed arterial perfusion sequence. Conjoined twins. Twin-twin transfusion syndrome. Stuck twin phenomenon. Twin entrapment.	Preterm delivery. Operative delivery. One of babies' death. Stillbirth. Twin entrapment.

Table 2. RCTs analyzed illustrating SET superiority over DET

Study	Criteria	Intervention	Result	Conclusion	Recommendation
Moustafa 2008	Young women, cryo-embryo transfer, 1 year follow up.	eSET vs. DET.	No significant difference in probability of live birth, higher rate of twins in DET group.	eSET should be 1st. line of choice.	Confirmation by larger randomized studies.
Fiddelers 2006	1st. IVF cycle in unselected patients.	Cost-effectiveness of one fresh cycle eSET vs. one fresh cycle DET.	Lower successful pregnancy rates for eSET, lower societal cost per couple after eSET.	One cycle eSET was less expensive and less effective compared to one cycle DET.	
van Montfoort 2006	Unselected patients, 1st. embryo transfer, availability of at least two 2PN zygotes.	eSET vs. DET	Ongoing PR after RCT-eSET was significantly lower compared with RCT-DET, and twin PR was reduced after RCT-eSET.	To avoid twin in IVF treatment, eSET should be applied in all patients, ongoing PR would be halved, transfer of one embryo in selected group of good prognosis leads to less drastic reduction but maintains twin PR.	
Gerris 1999	Women less than 34 years, 1st. IVF/ICSI, top quality embryo.	SET vs. DET	Lower IR, OPR, and limited DZ twin using SET.	Using SET and strict embryo criteria, an OPR similar to that in normal fertile couples can be achieved after IVF/ICSI, while limiting the DZ twin PR to its natural incidence of <1% of all ongoing pregnancies.	Fertility centers around the world, should by a mechanism of peer review, make sure that SET is accepted as routine policy in all centers.

3. Discussion

As illustrated in [Table 2] and according to the results, findings, outcomes, and recommendations by the articles we found and from data presented by others, eSET in fresh IVF/ICSI cycles most reduces twins pregnancy rate. Moreover, in the same time, (most probably) SET reduces implantation rate IR, pregnancy rate PR, and live birth rate LBR as well, when we compare it to the policy of DET. To achieve better results in applying the eSET policy which ends up with results comparable to the DET policy results, this might be met by involving fresh followed by frozen-thawed embryo transfer cycle.

Prioritizing the issue of multiple pregnancy reduction as a target to be achieved principally will situate the policy of eSET as a golden rule to be followed and this was evident as in all the clinical trials presented in [Table 2]. We found that the policy of eSET ended with less multiple pregnancy rates, other than one of the studies which addressed the main topic related to the cost-effectiveness of the eSET, the subject which again puts the eSET in favor of the DET which was found more expensive per couple as a final result. Consequently the authors tried to transmit the message that applying the policy of eSET is the preferred method to minimize the twinning or multiple pregnancy rates whether directly or indirectly. That display was associated with demonstrating that the results of certain articles after certain methods like cryo-embryo transfer cycle, 1-year follow-up period found that the probability of a live birth was not significantly different between the two groups of eSET and DET. All that ended by recommending eSET as first line of choice [25], away from that, recommendation of larger randomized studies was mentioned as a take home message.

In another article [12], the randomization was performed prior to the first embryo transfer, provided that at least two 2PN zygotes available and that gave the result of halving the ongoing pregnancy rate but lowering the twin pregnancy rate to 0% in the same time. That policy did not drop the idea of mentioning that the ongoing pregnancy rate after eSET and DET did not differ significantly (33.0 vs. 30.3).

Concerning the articles which supports the policy of SET with a strict criteria [7], we find that their results are promising as they concluded that by using SET and strict embryo criteria (presence of 4 or 5 blastomeres at day 2 and at least 7 blastomeres on day 3 after insemination, the absence of multinucleated blastomeres and <20% cellular fragments on day 2 and day 3 after fertilization). In the same time, implantation rate was insignificantly less in the SET group and the ongoing pregnancy rate OPR was significantly less, although they mentioned that by using SET and strict embryo criteria, an OPR similar to that in normal fertile couples can be achieved after IVF/ICSI while limiting the DZ twin to its natural incidence of <1%.

The other aspect taken in consideration is the cost-effectiveness of eSET compared to DET which is represented in one of the articles in Table 2 as a cost-effectiveness analysis alongside a randomized clinical trial [26]. The paper which endorses the other part of the story by pointing up a subject should not be away from our debate by analyzing the expenses of eSET in one cycle and expenses of DET in one cycle randomly in unselected patients and concluded that one cycle eSET was less expensive, but also less effective compared to one cycle DET.

Considering the four clinical trials presented in Table 2 and discussed previously, we locate eSET as preferred in the point of view of decreasing the twinning in ART treatment in all papers discussed previously related to this matter as a main subject. And also encouraging for it as a policy to be applied in cost-effectiveness point of view as well, one of these articles found it so far with no significant difference in probability of live birth compared to DET. On the other hand, lower successful PR, significantly lower OPR after RCT-eSET, and lower IR were found after eSET.

Away from analyzing these clinical trials we reviewed many other papers [27-51] under the same subject which ended up by finding that of the total number of 62 articles. After exclusion of 25 which were unrelated directly to the main subject or written in language other than English, or duplicated, remaining 37 to be explored meticulously, of these we found 28 (75.6%) mentioning that SET or eSET positively. We finally ended up finding it the best or a better way, or recommending it whether strongly or conservatively, 2 articles (5.40%) did not find SET or eSET a better way in comparison to DET in certain points of view, and 7 articles (18.9%) did not prefer it but did not deny it or they recommended for further larger trials.

In conclusion after what mentioned previously, we find eSET as a good policy to be followed extensively and we specify that it has a major role in minimizing twinning which is a major threat for ART treatment per se. In the same time, due to the results of other trials and the discrepancy between them as some did their trials without criteria whether for embryo or for patient's selection, and criteria's differentiation, we think that more evidences to be demonstrated in support of a certain policy is excellent idea. That special conclusion is due to the variation of the individualized protocols which could be expanded, so we recommend for larger clinical trials to prove for the effectiveness for it.

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