



## REVIEW



## Single-embryo transfer implies quality of care in reproductive medicine

**BIOGRAPHY**

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**KEY MESSAGE**

This review highlights that single-embryo transfer (SET) complies with important aspects of quality of care in reproductive medicine by encompassing safety, effectiveness, patient-centredness and efficiency, which leads to equity. SET should therefore be the standard of care in assisted reproductive technology.

**ABSTRACT**

This review appraises evidence on the difference between single- and double-embryo transfer (SET, DET) in assisted reproductive technology (ART) regarding the four healthcare quality dimensions most important to fertility patients and doctors. Regarding safety, not only does DET create the uncontested perinatal risks of twin pregnancies, but compelling evidence has added that singleton pregnancies after a vanishing twin also have poorer perinatal outcomes. SET is as effective as DET, as shown by meta-analyses of randomized controlled trials, comparing two cycles of SET versus DET and shown by cumulative live birth rates of entire ART trajectories of up to six cycles. Proposing SET, which is safer than DET and as effective, as the gold standard is not irreconcilable with patient-centred care if patients are thoroughly informed on the reasoning behind the proposition and welcomed to challenge whether it fits their personal values. The cost-efficiency of SET is clearly higher, which has even induced certain countries to start reimbursing ART on the condition that SET is used. In conclusion, SET should be the gold standard offered to all patients. The question is not whether to apply SET but how to apply it in terms of patient selection, patient-centred counselling and coverage of treatment.

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**KEYWORDS**

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## INTRODUCTION

The uptake of the single-embryo transfer (SET) strategy varies considerably within Europe, the USA and worldwide (Adamson and Norman, 2020; Dyer et al., 2016; Wyns et al., 2021). In addition, whether SET should be performed systematically to prevent twin pregnancies has led to lively debates at conferences and fierce opinion papers (Gleicher et al., 2017; Meldrum et al., 2018a, 2018b; Miller 2017; Van Voorhis et al., 2017).

Critically appraising (the interpretation of) the evidence on the differences between SET and double-embryo transfer (DET) is highly relevant as proponents and opponents of SET refer to the same healthcare quality dimensions and even evidence in their argumentation. Different conclusions on the healthcare quality dimension of 'safety' have been reached depending on whether ART twins are compared with naturally conceived twins (Helmerhorst, 2004) or with two singleton pregnancies (Sazonova et al., 2013). Proponents and opponents of SET have different interpretations of the same Cochrane analysis of Pandian and colleagues (Pandian et al., 2013) regarding the effectiveness of SET and DET. Opponents of SET argue that live birth rates per transfer are lower after SET than after DET (Gleicher et al., 2017) while proponents of SET focus on the lack of evidence of a significant difference in clinical pregnancy or live birth rates when comparing a single cycle of DET with repeated SET (Miller, 2017). Similarly, both opponents and proponents of SET refer to the healthcare quality dimension of 'patient-centredness' in their argumentation (Adashi and Gleicher, 2017; Meldrum et al., 2018b; Miller et al., 2017).

The debated safety, effectiveness and patient-centredness of SET are indeed the three most important quality dimensions according to patients and doctors from the field of assisted reproductive technology (ART; Dancet et al., 2013). Fourth in line according to patients and doctors is cost-efficiency (Dancet et al., 2013), which is especially relevant in this era of a global pandemic with economic implications. This review appraises the evidence on the difference between SET and DET regarding these four most topical healthcare quality dimensions: safety, effectiveness, patient-centredness and cost-efficiency.

## SAFETY

SET is associated with much lower rates of risky twin pregnancies than DET (Kamath et al., 2020; Pandian et al., 2013). Twin pregnancies result in a 5–10-fold increase in obstetric and perinatal risks and stillbirth is 2–3 times higher in twin than in singleton pregnancies, which is similar to twin pregnancies in general and twin pregnancies after ART (Pinborg et al., 2005a). Sazonova and colleagues (Sazonova et al., 2013) showed that the risks associated with a twin birth are substantially higher than those of two consecutive singleton births, which is a very fair comparison.

The prevalence of long-term neurodevelopmental disabilities including cerebral palsy is known to be higher in twins than in singletons in general (Lorenz et al., 2012), and also after ART (Goldsmith et al., 2018). A recent multinational cohort study from the Committee of Nordic ART and Safety (CoNARTaS) showed that the risk of cerebral palsy in children born after ART has more than halved from 1982 to 2015 concomitantly with a substantial decline in ART multiple birth rates (Spangmose et al., 2021). This decline in cerebral palsy in ART children cannot be explained by a decline in all children born as the relative odds of cerebral palsy in ART compared with spontaneously conceived children were higher in the period 1990–1993 than in the period 2011–2014 (adjusted odds ratio 2.76, 95% confidence interval [CI] 2.03–3.67 versus 1.39, 95% CI 1.01–1.87). Furthermore, maternal deaths, although only very rarely observed, are more prevalent in twin than in singleton pregnancies, including after ART (Braat, 2010; Santana, 2016). Overall, the steady decrease in multiple birth rates after ART during the last two decades (from 30% to 16.9% overall in Europe; De Geyter et al., 2020) significantly decreased the number of adverse obstetric and perinatal outcomes, especially in countries such as Finland and Sweden pioneering the implementation of SET (Henningsen et al., 2015; Opdahl et al., 2020).

Interestingly, adverse perinatal outcomes are observed in singleton births that originated from DET and twin pregnancies with a vanishing twin phenomenon, even if the spontaneous reduction occurred before gestational week 7–8 (Pinborg et al., 2005b) or later (Zhu Zhu et al., 2020). There are

data showing that the risk of cerebral palsy is also higher in cases of vanishing embryo(s) after DET or multiple embryo transfers compared with SET, although larger studies are needed (Goldsmith, 2018; Hvidtjorn et al., 2005, Hvidtjorn et al., 2010).

The safety risk associated with DET should especially be avoided in certain groups of women. In ageing women obstetric risks are even higher so DET should only be considered in women with multiple failed cycles and poorer embryo quality (Rissanen, 2019; Waldenström, 2017). Likewise, DET should be avoided in oocyte donation cycles due to the significantly increased risk of pre-eclampsia, which is even higher in oocyte donation twin pregnancies (Storgaard et al., 2017). DET should never be performed in women who have had a cervical conization as the risk of preterm birth is very high in twin pregnancies (Pinborg et al., 2015).

Female age has been a common argument in favour of DET; however it has been shown that the elective SET (eSET) policy can also be applied to women aged 36–39 years, reducing the risk of multiple birth and increasing the safety of ART in this age group (Veleva et al., 2006). Twin pregnancy, IVF and advanced maternal age are independently associated with adverse obstetric outcomes, and promotion of the eSET strategy is also needed to reduce multiple pregnancies following ART in women of advanced maternal age (Wang et al., 2021).

Poor embryo morphology has often been used as an argument in favour of DET, but the impact of blastocyst culture, vitrification and improved embryo morphology assessment on selection has further facilitated the eSET strategy. Data from all 124,700 complete IVF treatment cycles performed in Sweden during 2007–2017 showed that the cumulative live birth rate (CLBR) per oocyte aspiration increased significantly during the study period, from 27.0% to 36.3%, and from 30.0% to 43.3% if at least one embryo transfer was performed (Saket et al., 2021). During the same time period the percentage of SET in fresh cycles increased from 70% to 84%, and in frozen embryo transfer increased from 74% to 98%. A substantial increase in cumulative live birth rate (CLBR) took place despite an increasing

SET rate; hence blastocyst transfer, particularly when used in frozen embryo transfer cycles and in combination with vitrification, is an important contributor to the improved live birth rates over time. This provides the possibility that a lower number of oocyte aspirations will be needed to achieve a live birth and that there will be a shortened time to live birth in parallel with low multiple birth rates. Moreover, in preimplantation genetic testing for aneuploidies cycles with euploid blastocysts eSET should always be performed.

## EFFECTIVENESS

Randomized controlled trials (RCT) and meta-analyses thereof have found that a 1–2 cycle package with a SET strategy is no less effective than a cycle in which DET is allowed. McLernon and colleagues (McLernon *et al.*, 2010) performed a one-stage meta-analysis of individual patient data from randomized trials and concluded that eSET in fresh and associated frozen cycles results in a higher chance of delivering a term singleton live birth compared with DET. The Cochrane meta-analysis by Pandian and co-workers (Pandian *et al.*, 2013) and its update by Kamath and collaborators (Kamath *et al.*, 2020), comprising 14 RCT (2165 women) and 17 RCT (2505 women), respectively, concluded that a policy of repeated SET minimizes the risk of multiple pregnancy in couples undergoing ART without substantially reducing the live birth rate. More specifically, no evidence of a significant difference in clinical pregnancy or live birth rate between a single cycle of DET and repeated SET (two cycles of fresh SET, or a fresh SET and a frozen-thawed/vitrified-warmed SET) was found (Kamath *et al.*, 2020; Pandian *et al.*, 2013).

In contrast to RCT, the cohorts of national registries provide data on CLBR for entire ART trajectories including either multiple oocyte retrievals with attached embryo transfer cycles (complete cycles) or multiple embryo transfers. CLBR, which can be analysed with a conservative or an optimistic approach, was introduced by Malizia and colleagues (Malizia *et al.*, 2009) and answers the patient's question "What is my chance of achieving a live birth when I embark on an ART treatment?"

The CLBR across six complete cycles in the Belgian registry (2009–2012), in which

patients benefit from reimbursement on the condition of a balanced introduction of mandatory SET depending on the women's age, cycle rank and embryo quality, were compared with CLBR from other registries in order to evaluate a potential decrease in the CLBR (De Neubourg *et al.*, 2016). The CLBR across six complete cycles was 54.1% ( $\pm 0.44\%$  SE) in the conservative estimate and 76.3% ( $\pm 0.7\%$  SE) in the optimal estimate for all ages under 43 years old, which is comparable to the outcomes observed for other registries (De Neubourg *et al.*, 2016). However, the cumulative multiple live birth rate was 5.1% ( $\pm 0.19\%$  SE) in the conservative estimate and 8.6% ( $\pm 0.37\%$  SE) in the optimal estimate, which is spectacularly lower than in some countries such as USA and the UK (De Neubourg *et al.*, 2016).

A follow-up of this study, comparing the periods 2009–2012 and 2014–2017 of the Belgian registry observed that CLBR over six complete IVF/intracytoplasmic sperm injection cycles increased and cumulative multiple live birth rate decreased further over time (De Neubourg *et al.*, 2021). Interestingly, the decrease in CLBR over time was also statistically significant from the third complete cycle onwards, when SET was no longer mandatory, indicating that the field is increasingly applying SET on a voluntary basis (De Neubourg *et al.*, 2021).

The fact that DET is no more effective than SET is confirmed by the Society for Assisted Reproductive Technology (SART) generating 'big data' from disaggregated data from 26 countries (2017). More specifically, Adamson (2021) found, based on these SART data, that eSET resulted in a complete cycle live birth rate of 33.3%, and that elective DET resulted in a complete cycle live birth rate of 34.8%, while the multiple delivery rate was 2.2% for eSET and 26.2% for elective DET (Adamson, 2021).

Randomized trials are the ultimate proof of effectiveness but, to the current authors' knowledge, not many RCT have compared SET with DET in consecutive cycles, and the available RCT on the subject are older and are restricted to the first and second cycles in a good-prognosis patient population. CLBR calculations over large cohorts or registries aim to overcome the lack of randomized trials in consecutive cycles but are hampered by a potential change

in the profile of the patients, coverage policies, changes in laboratory practices such as the introduction of vitrification and blastocyst transfer, preimplantation genetic screening and the use of add-ons. Big data will also suffer from the above-mentioned limitations but will strive to diminish differences by analysing large numbers.

## PATIENT CENTREDNESS

Patient-centred care is guided by the values of (the group of) patients and is respectful of personal values with the aid of the crux of its approach: informed and shared decision making (Corrigan *et al.*, 2001; Weston, 2001). All individuals undergoing fertility treatment value informed decision making and some want to take part in decisions after having been informed and supported (Dancet *et al.*, 2011; Sol-Olafsdottir, 2013). This implies that patient-centred care is not irreconcilable with proposing a treatment option as the gold standard if two conditions are met. First, the proposed treatment must be more aligned with the values of the group of patients than its alternatives are. Second, patients must be thoroughly informed on the reasoning behind the proposition and welcomed to repeatedly challenge whether it fits their personal values.

SET can be proposed as the gold standard, as this review demonstrated that SET performs better than DET in terms of safety, and equally well in terms of effectiveness, the two most topical quality dimensions according to the group of fertility patients (Dancet *et al.*, 2013). Safety and effectiveness have indeed proven to be important for patients' preferences in choosing between SET and DET. Information on the safety risks of DET increase individuals' preference for SET (Griffin *et al.*, 2012; Murray *et al.*, 2004; Newton *et al.*, 2007; Ryan *et al.*, 2007), especially if patient testimonials are included (Hope and Rombauts, 2010).

Not claiming that DET is more effective than SET has been associated with more patients preferring SET (Newton *et al.*, 2007; Ryan *et al.*, 2007). A multifaceted intervention reimbursing an additional cycle in case of choosing SET (i.e. neutralizing patients' doubts on the equal effectiveness of SET and DET), besides providing safety information and decision support, increases the number of

patients choosing SET (*van Peperstraten et al., 2010*). Finally, a study aiming to elicit the 'true' preference between SET and DET of (this group of) patients (i.e. without the influence of counselling or notions of safety or effectiveness differences) found that the majority of participants expressing a preference between two theoretical options in the frame of a trial randomizing them between SET and DET chose a healthy singleton over a healthy twin (*Fiddlers et al., 2011*).

In order to offer the gold standard SET in a patient-centred manner, a tool is needed that facilitates the informed and potentially shared decision-making process, one which addresses all treatment characteristics valued by (the group of) fertility patients rather than only safety and effectiveness (*Dancet et al., 2014*). Fertility patients value the following 11 treatment characteristics: safety, effectiveness, costs, resemblance to natural conception, moral acceptability, the prospect of genetic parentage, a cure for infertility, conception at home, diagnostic insights, burden and timeliness (as reviewed by *Duthie et al., 2017; Hendriks et al., 2019*).

Besides information on safety and costs, information on the resemblance to natural conception and moral acceptability will point patients in the direction of SET. Singleton pregnancies are the norm in nature and SET safeguards the health and thereby welfare of vulnerable future children better than DET (*ESHRE Task Force on Ethics and Law, 2003; ESHRE Task Force on Ethics and Law, 2007*). Besides information on effectiveness, information on the four other treatment characteristics that do not differ between SET and DET is unlikely to affect patient's perspective. More specifically, SET and DET both offer the prospect of genetic parentage and neither offers a cure for infertility, conception at home or diagnostic insights. Whether information on the rarely examined treatment characteristic of 'timeliness' (*Sunkara et al., 2020*) and the multidimensional treatment characteristic of 'burden' will induce patients to challenge the gold standard of SET is unclear. Regarding burden, SET will not increase the burden of ovarian stimulation (*van den Wijngaard et al., 2014*) but it might increase the number of embryo transfers and thereby burden patients with additional clinic visits that

interfere with their social/work activities (*Palumbo et al., 2011*).

Individuals should be welcomed to challenge the gold standard of SET after being supported and informed using the decision-making tool and addressing all 11 treatment characteristics before every embryo transfer as patients' values can shift after having had an embryo transfer that did not result in pregnancy (*Fiddlers et al., 2011*).

Future studies into the patient-centredness of SET and DET should examine how many patients who are informed and supported by a novel tool addressing all 11 treatment characteristics, rather than only safety and effectiveness, challenge the proposed gold standard SET.

## COST-EFFICIENCY

The first study to compare real-life costs showed that the transfer of a single top-quality embryo is equally effective as but substantially cheaper than DET in women under 38 years of age going through their first ART cycle (*Gerris et al., 2004*). The total cost of DET was higher due to significantly higher neonatal costs rather than differences in maternal costs (*Gerris et al., 2004*). Next, a cost analysis was performed on the data of a randomized trial showing that the SET strategy, including one fresh SET and, if there was no live birth, one additional frozen-thawed SET, resulted in a live birth rate that was the same as that of DET, and a markedly reduced multiple birth rate (*Thurin et al., 2004*). The SET strategy proved superior to the DET strategy when the number of deliveries with at least one live-born child, an incremental cost-effectiveness ratio, and maternal and paediatric healthcare and productivity losses were taken into consideration (*Thurin-Kjellberg et al., 2006*).

Legislation, regulations and coverage that affect the uptake of SET strategies (*Maheshwari et al., 2011*) have the potential to cut costs, as demonstrated based on the data of several countries. Peeraer and colleagues (*Peeraer et al., 2017*) demonstrated that the Belgian legislation, combining the reimbursement of six ART cycles with a legally enforced reduction in the number of embryos transferred, resulted in a 50% reduction in multiple live birth rate and led to a 13% reduction in costs related to hospital

care. A study from Quebec (Canada) confirmed that the implementation of a public ART programme favouring SET not only sharply decreased the incidence of multiple pregnancy, but also reduced the cost per live birth, despite increased costs per cycle (*Velez et al., 2014*). In Australia, a voluntary shift to SET by clinicians and patients resulted in substantial savings in hospital costs, with much of the growth in ART use theoretically cross-subsidized by the move to safer embryo transfer practices (*Chambers et al., 2011*).

Crawford and colleagues (*Crawford et al., 2016*) used actual live birth rates from the USA National ART Surveillance System and estimated ART treatment and pregnancy/infant-associated medical costs. They concluded that performing sequential SET, when clinically appropriate, would theoretically reduce the total estimated ART treatment and pregnancy/infant-associated medical costs by reducing multiple births without lowering live birth rates (*Crawford et al., 2016*).

Van Heesch and co-workers (*Van Heesch et al., 2016*) have used the Markov model to analyse the cost-efficiency of eSET and DET and concluded that, from a short-term perspective (1 year), it is cost-effective to replace DET with SET; however when intermediate-term (5 years) and long-term (18 years) costs and consequences are incorporated, DET becomes the most cost-effective strategy, given a ceiling ratio of €20,000 per quality-adjusted life year gained. However, the model is based on a number of assumptions (relating to cancellations and the number of fresh and frozen-thawed cycles) and on data from different origins (studies and registries), completely ignoring that the fact that the outcome of different embryo transfer strategies cannot be constructed in order to give a clinically valid representation of possible outcomes.

A systematic review by Fiddlers and collaborators (*Fiddlers et al., 2007*) on the economic evaluation of SET versus DET concluded that eSET is only preferred from a cost-effectiveness point of view when it is performed in good-prognosis patients and when frozen-thawed cycles are included. If frozen-thawed cycles are excluded, the choice between eSET and DET depends on how much society is willing to pay for one



**FIGURE 1** Single-embryo transfer implies quality of care in reproductive medicine.

extra successful pregnancy. Interestingly, the cost-efficiency of SET has indirectly increased the uptake of ART in certain countries and thereby the equity of ART.

Coupling the reimbursement of the majority of ART-related costs to a reduction in the number of embryos transferred led to an increase in the uptake of ART by Belgian patients (*De Neubourg et al., 2013*). Velez and colleagues (*Velez et al., 2014*) confirmed that universal ART coverage on condition that SET was favoured increased access to ART in Quebec. In the USA, ART insurance coverage proved to be associated with increased utilization of eSET (SET + cryopreservation; adjusted odds ratio [aOR] 1.60, 95% CI 1.54–1.66; *Styer et al., 2016*) and increased utilization of ART (*Jain et al., 2002*). Not surprisingly given the increase in cost-efficiency and uptake of ART, three-quarters of responding members of the SART would want to comply with the use of SET in women under 38 years of age if this would be required for universal coverage (*Seifer et al., 2018*).

## CONCLUSIONS

This review concludes that SET should be the gold standard and that DET should only be performed on very rare occasions in high-quality reproductive medicine, because of reasons related to the four quality dimensions most important to fertility patients and doctors (**FIGURE 1**).

First and foremost, the short- and long-term outcomes of the children and of maternal health are compromised after DET, whether DET results in a twin or a singleton birth, and this is an even more dangerous situation for women with

perinatal health risk profiles. Choosing the safest option as the gold standard will not have any repercussions on ART success rates. DET is not more effective than SET according to meta-analyses of RCT focusing on 1–2 cycle packages, according to the CLBR reported by registries for entire ART trajectories of up to six complete cycles and according to big data from the SART. Proposing SET, which is safer than DET and just as effective, as the gold standard is not irreconcilable with patient-centred care if patients are thoroughly informed on the reasoning behind the proposition and are welcomed to challenge whether it fits their personal values. Finally, studies comparing the costs of an SET strategy with a DET approach, and assessing the cost savings of coupling the reimbursement of ART to an enforced SET strategy, have concluded that SET cuts costs.

The increasing implementation of vitrification techniques (when available), which results in higher survival and implantation rates (*Rienzi et al., 2017*), will support the widespread adoption of SET as the gold standard. The current authors want to stress that rather than debating its medically justified place in ART, the question is how to apply SET in terms of patient selection, patient-centred counselling and coverage of treatment.

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