Preterm birth

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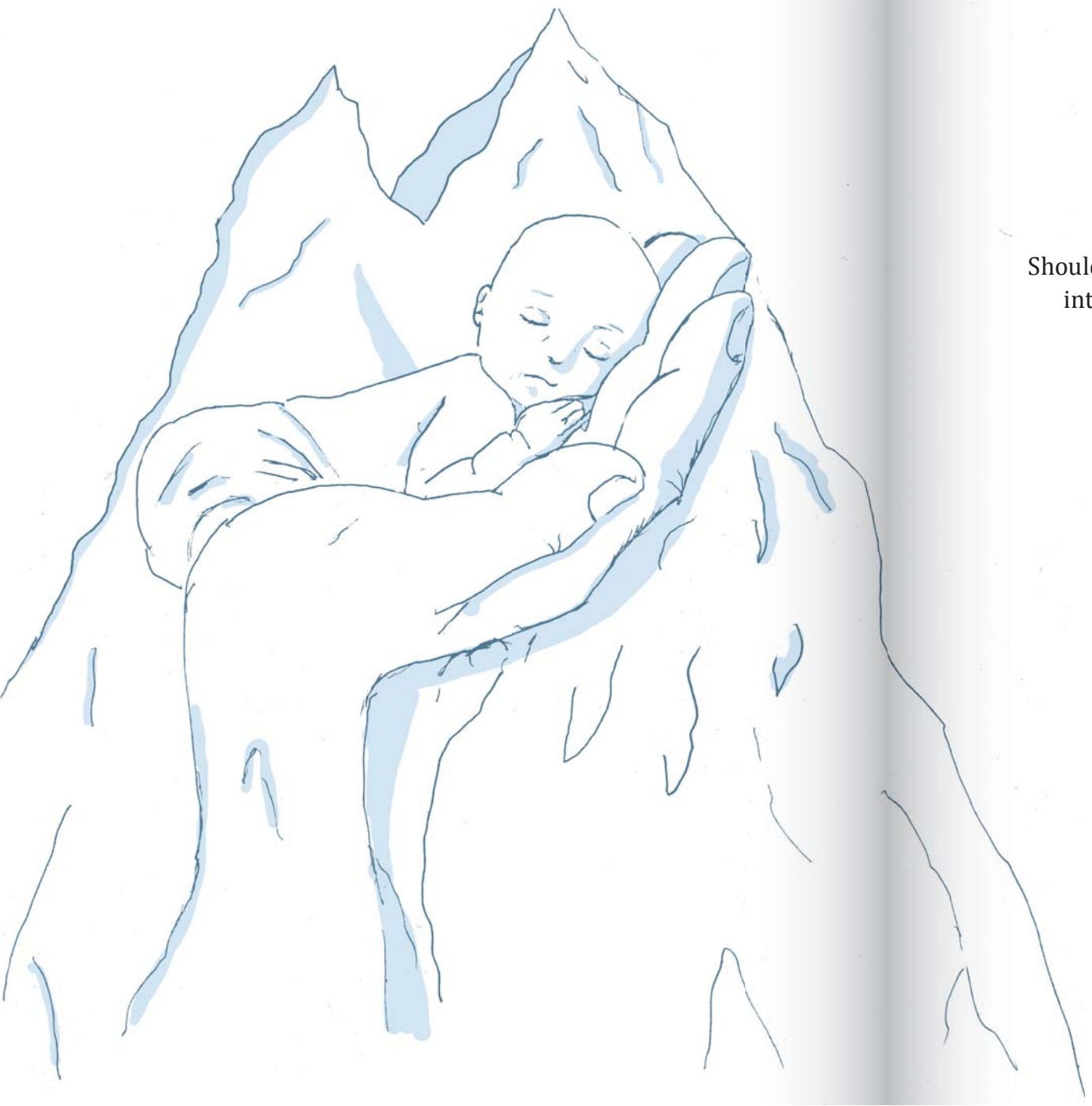

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Should the individual preterm birth risk be incorporated into the embryo transfer policy in in vitro fertilisation? A decision analysis

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ABSTRACT

Objective: To assess by proof of principle whether the individual risk for preterm birth (PTB) should be incorporated into the embryo transfer policy in in vitro fertilisation (IVF).

Design and setting: A theoretical decision analysis.

Methods and main outcome measures: A decision tree was built to compare the consequences of different chances of PTB on the outcome of single embryo transfer (SET) or double embryo transfer (DET) in patients with different prognosis of conception. Based on patient characteristics, three scenarios of prognosis of conception were considered and the consequences of SET and DET were calculated for different chances of PTB in these groups. The primary outcome was the health of the children born. Sensitivity analyses were performed for both prognosis for conception and chances of PTB.

Results: In women with good fertility prospects, one IVF cycle with DET increases the ongoing pregnancy rate (OPR) from 29 to 39% compared with SET, whereas the chances of poor neonatal outcome in these extra pregnancies range from 1.4 to 11% per pregnancy depending on the individual PTB risk. However, for women with poor fertility prospects, DET increases the OPR from 8 to 11% with minimal additional poor neonatal outcome, ranging from 0.3 to 4.0% per pregnancy for women with a low or high PTB risk, respectively. Our findings were robust in multiple sensitivity analyses.

Conclusion: In an IVF programme, the optimal embryo transfer strategy is dependent on the singleton and multiple pregnancy chances of a woman, but also on her PTB risk. In women with low PTB risk, DET increases the OPR for a small additional risk of neonatal complications. Our analysis pleads for a tailored management strategy, taking into account the personalised prognosis for (multiple) pregnancy and PTB.

INTRODUCTION

The aim of in vitro fertilistation (IVF) is to help couples with unfulfilled child wish in having a healthy baby. Because of the initial low success rates of IVF, doctors focussed on maximizing pregnancy chances by transferring multiple embryos, which resulted in an increased number of women with multiple pregnancies [1]. This was disconcerting as multiple pregnancies are associated with poor neonatal and maternal outcome. [2, 3]

At first, efforts were made to prevent high order multiple pregnancies by restricting transfer to two embryos. [4-6] When pregnancy rates after assisted reproductive technology (ART) had become higher, single embryo transfer (SET) was introduced. [7,8] A randomised study showed that women < 36 who had high quality embryos SET was not inferior to double embry transfer (DET), while it limited the twin rate to <1%. [9]

Aggregate as well as individual patient data meta-analysis of subsequent trials indicated that SET indeed reduced multiple pregnancy rates, but also decreased pregnancy rates per cycle. [10] Subsequent transfer of a single frozen thawed embryo or new fresh cycles resulted in comparable pregnancy rates, for much lower multiple pregnancy rates. [11, 12] This policy of SET is now enforced by law in for example Scandinavia, Belgium, Quebec and the Netherlands.

However, all trials included in the meta-analysis were limited to women with a good prognosis. [10] Although SET also prevents multiple pregnancies in couples with poor prognosis, it negatively affects pregnancy rates in these couples, while the risk of multiple pregnancy is low anyhow. [13] It should be noted here that it is not the multiple pregnancy itself that is the undesired outcome, but rather the increased risk of pregnancy complications related to multiple pregnancy, more specifically the risk of preterm birth (PTB) and subsequent neonatal morbidity and mortality. [14,15] As far as we know, the individual risk profile for spontaneous PTB of women entering an IVF program has never been taken into account. This might be a missed opportunity, since the individual risk of a woman for PTB differs, both based on female characteristics as well as obstetric history. [16-18] Such information, rather than the risk of multiple pregnancy alone, could possibly be used in the decision to apply SET or DET.

The aim of this study was to assess whether incorporation of an individual risk profile for PTB could affect the decision for SET or DET in an IVF program. A woman with a low risk of PTB and a poor prognosis on pregnancy might be better off with DET, while a woman at high risk of PTB and a good prognosis might benefit from SET.

MATERIAL AND METHODS

Decision tree model

We used a decision analytic approach to structure our problem. Decision modelling allows clinicians to compare the effects of alternative management strategies in the absence of clinical trials. [19,20] We created a decision tree to evaluate the effects of SET and DET on ongoing pregnancy rates (OPR), percentage of singleton and multiple pregnancies, term and PTB rates and outcome of the child, taking into account both prognosis for conception and subsequent risk of PTB (figure 1). The decision tree has two parts. The first part consists of characteristics that determine the risk profile which leads, based on prognosis of conception (good, intermediate and poor) and risk of preterm birth (PTB) (high intermediate and low), to nine categories of couples. The second part is the decision for the intervention (SET or DET) for each category of patients and the subsequent results that follow from the decision.

We analysed a woman with respectively a good, intermediate and poor prognosis for conception and varied the risk of spontaneous PTB, based on her obstetric history (i.e. nulliparous, previous singleton PTB, previous term delivery of a twin).

Definitions

An ongoing singleton pregnancy was defined as one gestational sac with fetal heart activity observed at least 10 weeks after embryo transfer, while an ongoing twin pregnancy was defined as two gestational sacs with fetal heart activity present at at least 10 weeks of gestation. PTB was defined as delivery before 37 weeks. In the assessment of outcomes, twins were considered a single count.

Assumptions

The assumptions made in the decision analysis are shown in Table 1. The probability of ongoing singleton pregnancy and ongoing twin pregnancy after SET and DET was estimated using an internally and externally validated prediction model for IVF-outcome from Hunault. [21] This model includes five predictors, of which three, i.e. number of retrieved oocytes, developmental stage and morphology grade of the best and second embryo were selected after multivariate regression analysis with a stepwise selection procedure, while two others, female age and day of transfer, were added on clinical grounds.

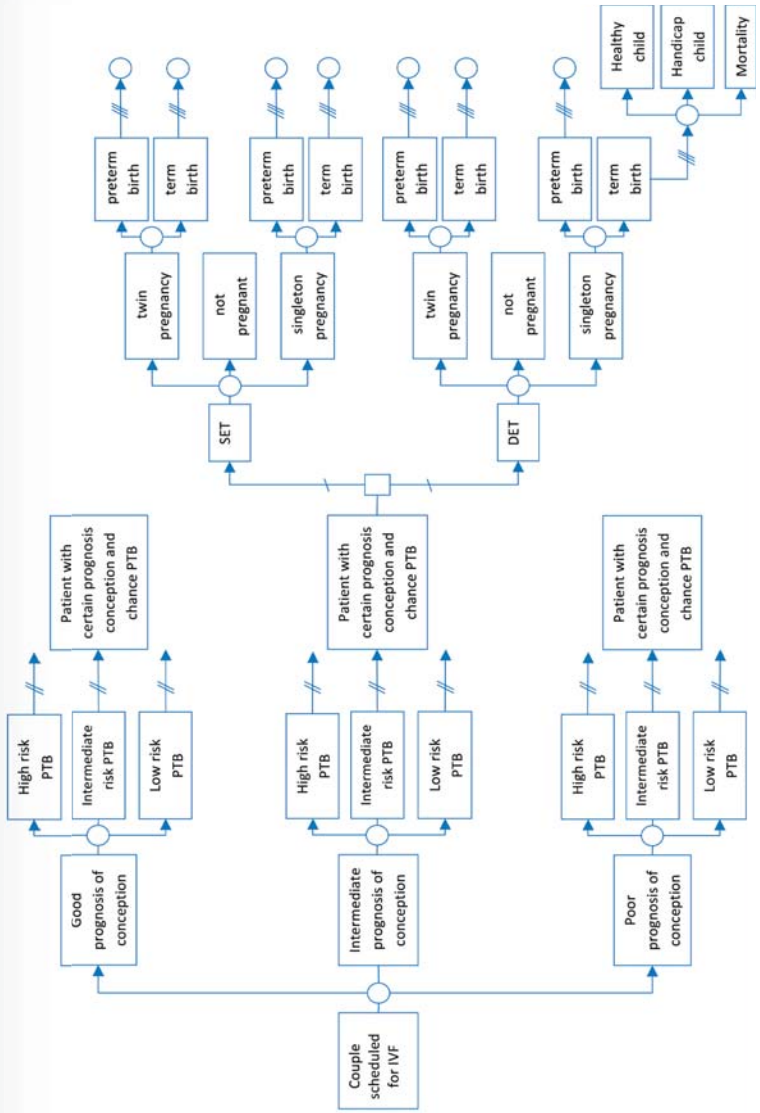

Figure 1: Decision tree
The decision tree has two parts. First, characteristics determine the risk profile which leads, based on the prognosis of conception (good, intermediate and poor) and risk of preterm birth (PTB)(high, intermediate and low), to nine categories of couples. The second part is the decision for the intervention (single or double embryo transfer, SET or DET) for each category of patients and the subsequent results that follow from the decision. The prognosis for conception after in vitro fertilisation (IVF) is based on the model of Hunault et al. [21] which predicts the outcome of IVF (i.e. age, quality of embryos), whereas the risk of PTB, for example, is based on obstetric history (i.e. first pregnancy, previous term or preterm). [18] Based on these characteristics, a decision must be made on either SET or DET. Depending on the prognosis of conception, the SET or DET strategies lead to certain singleton and twin pregnancies, which subsequently result in specific percentages of term and preterm births, which in the next step result in healthy, handicapped or dead children.

Using the model of Hunault, the prognosis of conception resulting in an ongoing pregnancy was classified in three categories, i.e. women with a good prognosis of conception (relative young age and two high quality embryos), women with an intermediate prognosis of conception (intermediate age and intermediate scores for the best two embryos) and women with a poor prognosis of conception (relative old age and poor quality of embryos). We chose these three categories as a proof of principle to show the influence of different prognosis for pregnancy, but daily practice doctors can use the model per patient to predict in a more accurate way. Furthermore the individual preconceptional risk for spontaneous PTB was classified as low, normal or high. A normal risk of PTB was present in nulliparous women, an increased risk for PTB was considered to be present when a woman had suffered previous PTB in a singleton pregnancy, while a decreased risk for PTB was considered to be present when a woman had delivered a twin pregnancy at term. [18] These assumptions are based on an extensive systematic review from Kazemier et al. in which pooled estimate OR's were calculated for spontaneous PTB in the general population. [18] The subsequent rates for perinatal morbidity and mortality resulting from PTB and term birth were obtained from the Perinatal Registry in The Netherlands (PRN) from 1999-2007 by Schaaf et al. [22] This is a cohort of 840.421 Caucasian women with spontaneous onset of birth of a singleton of whom 44.790 suffered PTB. Neonatal mortality was defined as intrapartum or neonatal mortality within 28 days after preterm birth. Adverse neonatal outcome/handicap was defined as intraventricular hemorrhage, bronchopulmonary dysplasia, infant respiratory distress syndrome or neonatal sepsis.

Table 1: Assumptions on conception rates, preterm birth risk and condition of the child considered in the analyses

Success rate after IVF [21]					
Prognosis	Characteristics	Transfer	OPR	Singleton	Twin
Good	Young age, good embryo's	SET	29%	28.7%	0.3%
		DET	39%	20%	19%
Intermediate	Intermediate age and embryo's	SET	14%	13.9%	0.1%
		DET	24%	19%	5%
Poor	Older age poor embryo's	SET	8%	7.9%	0.1%
		DET	11%	10%	1%
Risk of spontaneous PTB [18, 22]					
		Singleton pregnancy		Multiple pregnancy	
First pregnancy		5.2%		41.9%	
High (after previous preterm singleton)		19.5%		57%	
Low (after previous term twin)		1.3%		5%	
Condition of the child [22]					
		Healthy	Handicapped	Death	
Term birth		99.6%	0.3%	0.1%	
Preterm birth		87.5%	9.8%	2.7%	

PTB = Preterm birth, SET= Single embryo transfer, DET= double embryo transfer, OPR = ongoing pregnancy rate.

Statistical analyses

From the information in Table 1, it follows that for the baseline case, i.e. a nulliparous woman with good prognosis for conception undergoing SET, the 29% ongoing pregnancy rate (28.7% singleton and 0.3% twin) results in a PTB risk of 1.6% and a term birth rate of 27.4%. The 1.6% PTB risk is calculated from a 28.7% OPR * 5.2% PTB = 1.49% for singletons and a 0.3% OPR * 41.9% PTB = 0.12% for twins. Subsequently, the risk of a healthy child, a child with serious morbidity or a dead child was calculated from term and PTB rates (chances of a healthy child, a child with serious morbidity and a dead child of 27.29 % (27.4*0.996), 0.08% (27.4*0.003) and 0.03% (27.4*0.001) after term delivery and of 1.4% (1.6*0.875), 0.16% (1.6*0.098) and 0.043% (1.6*0.027) after preterm delivery) (22). This results for the woman in the baseline case scenario in an overall probability of a healthy child, a child with serious morbidity or a dead child of 28.69%, 0.24% and 0.07%, respectively. In a similar way, we calculated the expected outcome for nulliparous women for a scenario with a moderate and a poor chance of conception, and for women with low and high risk of PTB.

Finally, to express the relative safety of a strategy, we calculated the term/preterm ratio as the ratio from the number of children born at term and the number of children born preterm. In the woman in our base case, the term/preterm ratio was 17, calculated as a 27.4% probability of a child born at term versus a 1.6% probability of a child born preterm. As reference, for the overall Caucasian population delivering a child in The Netherlands for example, the ratio is 18.2, calculated as the ratio of 94.8% term deliveries and 5.2% preterm deliveries (23-24). The term/preterm ratio decreases when the percentage of PTBs increases compared to term births, indicating an unsafe risk profile, while a higher ratio indicates an increase in percentage of term births compared to PTB, thus reducing perinatal morbidity and mortality thereby indicating relative safety. We used Microsoft Excell 2013 for our analysis.

Sensitivity analysis

To explore the impact of variation in our assumptions, we performed multiple sensitivity analyses. In the first sensitivity analysis we used the upper and lower limit of the 95% confidence interval for the risk of PTB as previously reported (Table S1). [18] Subsequently, we varied the pregnancy chances for the several subgroups, as well as the risks of serious child morbidity and perinatal mortality.

RESULTS

The impact of the choice for SET or DET on the singleton and multiple pregnancy rates, the subsequent chances of term and PTB's and the condition of the children born from those pregnancies, stratified by prognosis for conception, in a woman with different risk profiles for spontaneous PTB based on obstetrical history is shown in Table 2.

Good prognosis for conception

In a woman with a good prognosis for conception, DET provides higher OPR than SET, i.e. 39% versus 29% (Table 2).

In case this woman has a high risk of spontaneous PTB, her absolute chance of term and preterm birth after SET is 23.2% and 5.8% respectively. Subsequent probabilities of the birth of a healthy child, the birth of a baby with serious morbidity and perinatal mortality are 28.2%, 0.6%, and 0.2%, respectively. The accompanying term/preterm ratio is 4.0.The same woman undergoing DET has term and preterm delivery rates of 24.3% and 14.7%, respectively, resulting in

absolute chances of a healthy child, serious neonatal morbidity and perinatal mortality of 37.1%, 1.5% and 0.4%, respectively. Her accompanying term/preterm rate decreases to 1.7.

These data imply that the additional 10% OPR of DET over SET, results in an additional 8.9% chance of birth of a healthy child, 0.9% chance of a baby with serious morbidity and 0.2% of a dead child. Thus, the chance that the additional child born after DET compared to SET is healthy is 89% (8.9/10) while the chance of a poor outcome (i.e. serious morbidity or death) in this additional child is 11% (1.1/10).

If a woman with a similar good prognosis for conception has a normal risk of PTB (i.e. if she would be nulliparous), DET would also lead to a 10% additional chance of ongoing pregnancy, with an additional probability of 9.06% of a healthy child, 0.74% of a baby with serious morbidity and 0.20% of a dead child. The chance that the additional born child by DET compared to SET is healthy is 90.6% (9.06/10) while the chance of a poor outcome (i.e. serious morbidity or death) in this additional child is 9.4% (0,94/10).

Finally, if the same woman with a good prognosis for conception has a low risk of PTB, the additional 10% higher OPR from DET will be 9.86% healthy, 0.11% with serious morbidity and 0.03% deaths. Thus, the chance that the additional child born after DET compared to SET is healthy is 98,6% (9.9/10) while the chance of a poor outcome (i.e. serious morbidity or death) in this additional child is 1.4% (0.14/10). Thus, in a woman with a good prognosis for conception the chance of a poor outcome of the extra child born because of DET compared to SET ranges from 11% for a woman with a high risk of PTB to 1.4% for a woman with a low risk of PTB.

Intermediate prognosis for conception

The results in a woman with an intermediate prognosis of conception for different risk profiles of PTB are also shown in Table 2. The OPR again is 10% higher after DET compared to SET, with absolute percentages of 24% and 14%, respectively. If this woman has a normal risk profile for PTB, which will be the case in a substantial part of the total IVF population, DET will result in an additional probability of 9.68% for a healthy child, 0.25% for a child that suffers serious morbidity and 0.07% for a child that will die. Thus, the chance that the additionally born child due to DET as compared to SET is healthy is 96.8% (9.68/10).

For women with an intermediate prognosis for conception, the chances that an extra child born by DET compared to SET has a poor outcome ranges between 5% in a women with a high risk of PTB to 0.8% in women with a low risk of PTB.

Poor prognosis for conception

Finally, we assessed women with poor prognosis for conception, who have OPRs of 8% and 11% after SET and DET, respectively. For a woman with a low risk of preterm birth after SET 0.1% out of 8% of the children will be born preterm, versus 0.2% out of 11% after DET. The associated difference in children with a serious morbidity or dead children out of the 3% extra born children by DET will be 0.02% and 0.01% respectively, indicating that 99.7% of the extra born children by DET will be healthy. The chance of poor outcome in this group is therefore 0.3%. The accompanying term/preterm ratio is 60 for DET and 74 for SET.

Twin rates and term/preterm ratio

Both the OPR and percentage of twins were higher after DET in all groups of patients (Table 2), but the rate of multiple pregnancies depended on the prognosis for conception and varied from 9% in women with poor prognosis for conception to 48.7% in women with a good prognosis for conception. The PTB chances ranged from 0.1% to 14.7% and term birth chances ranged from 6.4% to 37.8%.

The term/preterm ratios for all subgroups are shown in table 2. In women with a normal risk of PTB, SET results in a term/preterm ratio of 17, comparable to the mean term/preterm ratio of 18.2 in The Netherlands. Obviously, DET results in a low term/preterm ratio compared to the standard ratio for women with a normal risk of PTB. In women with a low risk of PTB, the term/preterm ratios of both SET and DET are higher than the standard with 60 for DET and 74 for SET.

Sensitivity analysis

Figure 2 shows the result of a one-way sensitivity analysis in which we varied the ongoing pregnancy rates between 2% and 45%. The figure shows that for women at low risk for preterm birth (green lines), the safety for both SET and DET is acceptable over the whole range of pregnancy rates, since the term/preterm ratio remained above 20. For women at high risk for preterm birth (red lines), the preterm/term ratio is unfavourable for SET and DET, but specifically for DET in women with a good prognosis for conception. For women at intermediate risk (blue lines), the SET strategy has an acceptable safety profile (term/preterm ratio 18) while DET has an acceptable safety profile until pregnancy rates of 15%, to deteriorate thereafter. The figure also shows the position of patients with a PTB risk between intermediate and low, for example a woman with a previous singleton birth at term (purple), and between intermediate and high, for example a woman with a previous twin preterm birth or women with previous cervical surgery (orange). Multiple sensitivity analyses varying chances of PTB showed our results to be stable over a large number of ranges (data not shown).

Table 2: Outcomes of a SET and DET policy in women with different prognoses and different risk profiles for spontaneous PTB

Prognosis for conception	Risk profile PTB	Transfer	Type of pregnancy			Duration of pregnancy				Child	
			OPR	Singleton	Twin	Term birth	PTB	Term/ PTB ratio	Healthy	Handicap	Death
Good (First pregnancy)	High	SET	29%	28.7%	0.3%	23.2%	5.8%	4.0	28.2%	0.6%	0.2%
		DET	39%	20.0%	19.0%	24.3%	14.7%	1.7	37.1%	1.5%	0.4%
	Normal	SET	29%	28.7%	0.3%	27.4%	1.6%	17	28.7%	0.2%	0.07%
		DET	39%	20.0%	19.0%	30.0%	9.0%	3.3	37.8%	1.0%	0.3%
	Low	SET	29%	28.7%	0.3%	28.6%	0.4%	74	28.8%	0.1%	0.04%
		DET	39%	20.0%	19.0%	37.8%	1.2%	31	38.7%	0.2%	0,07%
Intermediate (First pregnancy)	High	SET	14%	13.9%	0.1%	11.2%	2.8%	4.0	13.6%	0.3%	0.09%
		DET	24%	19.0%	5.0%	17.5%	6.6%	2.7	23.1%	0.7%	0.2%
	Normal	SET	14%	13.9%	0.1%	13.2%	0.8%	17	13.9%	0.1%	0.03%
		DET	24%	19.0%	5.0%	20.9%	3.1%	6.8	23.5%	0.4%	0,1%
	Low	SET	14%	13.9%	0.1%	13.8%	0.2%	74	13.9%	0.06%	0.02%
		DET	24%	19.0%	5.0%	23.5%	0.5%	47	23.8%	0.1%	0.04%
Poor (First pregnancy)	High	SET	8%	7.9%	0.1%	6.4%	1.6%	4.0	7.8%	0.2%	0.05%
		DET	11%	10.0%	1.0%	8.5%	2.5%	3.4	10.7%	0.3%	0.08%
	Normal	SET	8%	7.9%	0.1%	7.6%	0.5%	17	7.9%	0.07%	0.02%
		DET	11%	10.0%	1.0%	10.1%	0.9%	11	10.8%	0.1%	0.04%
	Low	SET	8%	7.9%	0.1%	7.9%	0.1%	74	8.0%	0.03%	0.01%
		DET	11%	10.0%	1.0%	10.8%	0.2%	60	10.9%	0.05%	0.02%

Because of rounding decimals, numbers do not always add up correctly.
PTB = Preterm birth, SET= Single embryo transfer, DET= double embryo transfer, OPR = ongoing pregnancy rate.

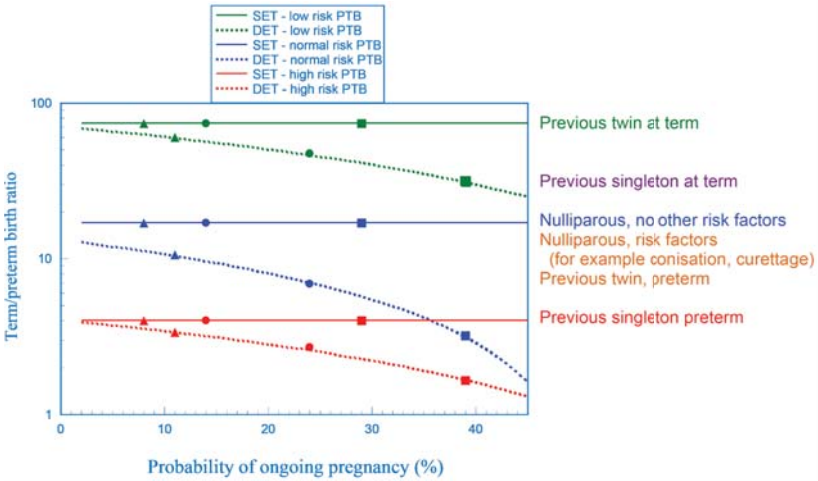

Figure 2: The term/preterm ratio is displayed as a function of the ongoing pregnancy rate (OPR) for both single embryo transfer (SET) and double embryo transfer (DET) taking the individual risk of preterm birth (PTB) into account.
The triangles represent a woman with a poor prognosis for conception, the circles a woman with an intermediate prognosis for conception and the squares a woman with a good prognosis for conception. From the green lines, it can be derived that, for women with a low risk of PTB, both SET and DET are safe compared with the standard, whereas DET has a higher OPR relative to SET for women with the same prognosis (i.e. 24% versus 14% for women with intermediate prognosis for conception [green circles]). For women at high risk for preterm birth (red lines), the preterm/term ratio is unfavourable for both SET and DET, but most unfavourable for the DET strategy and high probabilities of ongoing pregnancy. For women at intermediate risk of PTB (blue lines), the SET strategy is safe compared with the standard, whereas DET has an acceptable safety compared with the standard up to pregnancy rates of 10%, and deteriorates thereafter. The figure also shows the position of patients with a PTB risk between intermediate and low, for example a woman with a previous singleton birth at term (purple), and between intermediate and high, for example a woman with a previous preterm twin or women with previous cervical surgery (orange).

DISCUSSION

Main findings

In this decision analysis we showed that the balance between effectiveness and safety of SET and DET is not only dependent on the pregnancy chances determined by embryo quality and female age, but also on the PTB risk of the woman with unfulfilled child wish. In women with good fertility prospects, one IVF cycle with DET increases the pregnancy chances with 10% compared to SET, while the chance of poor neonatal outcome in these extra pregnancies ranges from 1.4 to 11% depending on the individual risk for PTB. On the other hand, for women with

poor fertility prospects DET increases the pregnancy rates from 8 to 11%, with minimal additional poor neonatal outcome, ranging from 0.3-4.0% for women with a low or high risk of PTB, respectively. Our findings were robust in multiple sensitivity analyses.

Strengths and limitations

Our study is not without limitations. First, we used a decision analytic approach, in which we integrated data from cohort studies. Hunaults' model is based on cohort data, thus carrying the risk of selection bias. Although this model has been externally validated, probabilities used might not perfectly represent the 'real' success rates of IVF that would have been observed in randomised comparisons of SET or DET. These success rates are also dependent on the clinic where the IVF procedure is performed. Unfortunately, randomised comparisons that show that SET is equally effective as DET are only available in women with a goodfertility prognosis. [10]

Second, we used prematurity dependent risks on neonatal morbidity and mortality that were based on singleton pregnancies. These risks could underestimate the percentage of serious neonatal morbidity in multiple pregnancies, as for example the average birth weight of twins is lower compared to singletons at the same gestational age. However, in a recent Scandinavian cohort study among IVF twin pregnancies the composite outcome of serious morbidity was 2.3%, the combined stillbirth and 1 year infant mortality rate was 1.4% while PTB (<37 wks) and very PTB rates (< 32 wks) were 47% and 7.5%, respectively. [15] In fact, we assumed higher rates for serious morbidity and perinatal mortality among twins.

Third, prediction of PTB before deciding on SET or DET remains a challenge. Widely accepted predictors as cervical length are obviously not available preconceptionally and the accuracy of PTB risk reported in the literature varies widely across studies in nulliparous women, in multiple pregnancy or in women with a history of PTB. Nevertheless, even in nulliparous women, who constitute a large percentage of the IVF population, prediction of PTB is possible in a range from 7.5% to 32.5%. [17] Factors such as ethnicity, age, smoking, blood pressure and diabetes all might play a role. Furthermore, it is known that induced abortion, curettage and treatment for precancerous changes of the cervix increase the risk of preterm birth. [25,26] Further research is needed to optimise the preconceptional prediction of PTB. Our decision analysis focuses on spontaneous PTB. As stated above, our study is a proof-of-principle study, making detailed calculations for each of these issues beyond the scope of this paper. Obviously, the risk for iatrogenic PTB is another clinical situation in which the decision for IVF-SET or IVF-DET can influenced by the subsequent risk of complications such as pre eclampsia (PE) or

intra uterine growth restriction (IUGR). For some of these diseases, there are many well known risk factors, such as chronic hypertension. A recent meta-analysis showed that the risk of PE is increased with a RR of 7.7 in women with chronic hypertension. [27] Consequently, similar scenarios as the one shown for women with previous preterm birth, can be made for women with previous PE or IUGR, not only using chronic hypertension, but also biomarkers for PE, growth restriction and spontaneous preterm birth which could be included in individualization of the embryo transfer policy. [28] Thus, although improvement in the preconceptional prediction of spontaneous and iatrogenic PTB is probably possible, the importance of our study is that it demonstrates the principle that individual PTB risk can affect the embryo transfer strategy.

Fourth, we decided to consider the birth of twins a single count. This approach obviously generates a devaluation of the outcome of DET, as the birth of two healthy children from one twin pregnancy is counted as a single success, but the same principle applies to a poor outcome. We did so, as studies comparing the valuations of twin children as compared to singletons are lacking.

Interpretation

The current implementation of SET in IVF as a general rule, and not in an individualized manner forgets to individualize the prognosis for conception and does not take in account the magnitude and seriousness of the problem we try to avoid, i.e. handicapped or dead children born from twin pregnancies. This is disconcerting as the effectiveness of SET compared to DET has only been assessed in women with a good prognosis and in addition, twin pregnancies itself are seen as a negative outcome of IVF instead of the associated risk of PTB and subsequent complications. [14] The consequences of the universal implementation of SET affects pregnancy chances of older women and women with embryos of poor quality, even if their individual risk of preterm birth is low. These women may thus fail to reach a pregnancy after SET, even though their risk on a complication from a twin pregnancy might in fact be very low. On the other hand, due to a lack of reimbursement of IVF in a wide range of countries, including the USA and the UK, DET might be applied in women with good fertility prospects and a high risk of PTB, leading to –avoidable- preterm birth with subsequent complications.

The importance of our approach is that we integrated pregnancy chances after SET and DET in an IVF program with PTB risks and subsequent pregnancy outcomes in singleton and twin pregnancies, thus addressing embryo transfer policy in a more holistic way. We have combined the individual profile that is aimed by individualized or precision medicine, with the outcome of interest for the subfertile

woman, i.e. help her to fulfill her desire for motherhood, preferably by children without complications. [29]

Other studies have also tried to individualize the decision between SET and DET based on the PTB risk. Female age was recently demonstrated to affect the outcome of SET or DET, and should therefore be a factor in the decision for SET or DET. [30] In both older and younger women DET led to better live birth rates than SET, while DET was less likely to result in PTB or low birth weight in older women.

CONCLUSION

Summarizing, our study shows that for women with good prognosis and high risk of PTB the transfer policy should be SET. For women with poor prognosis and low risk of PTB on the other hand, DET seems to be more effective in reaching a pregnancy with low risks for perinatal morbidity and mortality in case of a twin pregnancy. In our view, the optimal embryo transfer strategy should be based on the individual prognoses for pregnancy, multiple pregnancy and for PTB. We feel that a universal indiscriminate SET policy wrongfully and unnecessary prevents pregnancies in women with a poor prognosis of pregnancy, and plead for a personalized management strategy for SET or DET, taking into account both fertility and obstetric prognostic profiles.

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SUPPLEMENTARY FILES

Table SI: Sensitivity analysis of outcomes of a SET and DET policy in women with different prognoses and different risk profiles for spontaneous PTB, varying risk of PTB based on lower and upper 95% CI [18, 22]

			Type of pregnancy			Duration of pregnancy: mean (upper and lower 95% CI)			Child: mean (upper and lower 95% CI)		
Prognosis for conception	Risk PTB	ET	OPR	Singl	Twin	Term birth	PTB	Term/ PTB ratio	Healthy	Handicap	Death
Good	High	SET	29%	28.7%	0.3%	23.2% (23.1-23.4)	5.8% (5.9-5.6)	4.0 (3.9-4.1)	28.2% (28.2-28.2)	0.6% (0.6-0.7)	0.2% (0.2-0.2)
		DET	39%	20.0%	19.0%	24.3% (23.3-25.3)	14.7% (15.7-13.7)	1.7 (1.5-1.9)	37.1% (36.9-37.2)	1.5% (1.4-1.6)	0.4% (0.4-0.5)
	Normal	SET	29%	28.7%	0.3%	27.4% (27.2-27.5)	1.6% (1.8-1.5)	17 (15.4-18.8)	28.7% (28.7-28.7)	0.2% (0.2-0.3)	0.07% (0.07-0.07)
		DET	39%	20.0%	19.0%	30.0% (29.5-30.5)	9.0% (9.5-8.5)	3.3 (3.1-3.6)	37.8% (37.7-37.8)	1.0% (0.9-1.0)	0.3% (0.3-0.3)
	Low	SET	29%	28.7%	0.3%	28.6% (28.3-28.8)	0.4% (0.7-0.2)	74 (43-121)	28.8% (28.8-28.9)	0.1% (0.1-0.2)	0.04% (0.04-0.05)
		DET	39%	20.0%	19.0%	37.8% (37.1-38.4)	1.2% (1.9-0.6)	31 (19.9-60.4)	38.7% (38.6-38.8)	0.2% (0.2-0.3)	0.07% (0.06-0.09)
Intermediate	High	SET	14%	13.9%	0.1%	11.2% (11.2-11.3)	2.8%(2.8-2.7)	4.0 (3.9-4.1)	13.6% (13.6-13.6)	0.3% (0.3-0.3)	0.09% (0.08-0.09)
		DET	24%	19.0%	5.0%	17.5% (17.1-17.8)	6.6% (6.9-6.2)	2.7 (2.5-2.9)	23.1% (23.1-23.2)	0.7% (0.7-0.7)	0.2% (0.2-0.2)
	Normal	SET	14%	13.9%	0.1%	13.2% (13.1-13.3)	0.8% (0.9-0.7)	17 (15.4-18.8)	13.9% (13.8-13.9)	0.1% (0.1-0.1)	0.03% (0.03-0.04)
		DET	24%	19.0%	5.0%	20.9% (20.7-21.1)	3.1% (3.3-2.9)	6.8 (6.3-7.4)	23.5% (23.5-23.6)	0.4% (0.4-0.4)	0,1% (0.1-0.1)
	Low	SET	14%	13.9%	0.1%	13.8% (13.7-13.9)	0.2% (0.3-0.1)	74 (43-121)	13.9% (13.9-13.9)	0.06% (0.05-0.07)	0.02% (0/02-0.02)
		DET	24%	19.0%	5.0%	23.5% (23.2-23.7)	0.5% (0.8-0.3)	47 (29-86)	23.8% (23.8-23.9)	0.1% (0.1-0.2)	0.04% (0.04-0.04)
Poor	High	SET	8%	7.9%	0.1%	6.4% (6.4-6.4)	1.6% (1.6-1.6)	4.0 (3.9-4.1)	7.8% (7.7-7.8)	0.2% (0.2-0.2)	0.05% (0.05-0.05)
		DET	11%	10.0%	1.0%	8.5% (8.4-8.6)	2.5% (2.6-2.4)	3.4 (3.2-3.5)	10.7% (10.6-10.7)	0.3% (0.3-0.3)	0.08% (0.07-0.08)
	Normal	SET	8%	7.9%	0.1%	7.6% (7.5-7.6)	0.5% (0.5-0.4)	17 (15.4-18.8)	7.9% (7.9-7.9)	0.07% (0.06-0.07)	0.02% (0.02-0.02)
		DET	11%	10.0%	1.0%	10.1% (10.0-10.3)	0.9% (1.0-0.9)	11 (9.9-11.7)	10.8% (10.8-10.9)	0.1% (0.1-0.1)	0.04% (0.03-0.04)
	Low	SET	8%	7.9%	0.1%	7.9% (7.8-7.9)	0.1% (0.2-0.1)	74 (43-121)	8.0% (8.0-8.0)	0.03% (0.03-0.04)	0.01% (0.01-0.01)
		DET	11%	10.0%	1.0%	10.8% (10.7-10.9)	0.2% (0.3-0.1)	60 (36-104)	10.9% (10.9-10.9)	0.05% (0.04-0.06)	0.02% (0.01-0.02)

Because of rounding decimals, numbers do not always add up correctly.
PTB = Preterm birth, ET = embryo transfer, Singl = singleton, SET= Single embryo transfer, DET= double embryo transfer, OPR = ongoing pregnancy rate