Contribution of cryopreservation in a mandatory SET policy: analysis of 5 years of application of law in an academic IVF center

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Received: 3 July 2011 / Accepted: 5 September 2011 / Published online: 1 October 2011
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Abstract

Objective To analyse treatment outcomes after SET law enforcement and to evaluate the contribution of cryopreservation in a SET policy.

Material Embryo transfer cycles performed after the law enforcement (SET period) was retrospectively compared to the cycles performed before the law enforcement (DET period).

Results Pregnancy and delivery rates after fresh transfer of SET and DET periods were comparable (31.7% versus 33.3% and 24.5% versus 26.2%, respectively, NS). Overall twin delivery rate is significantly decreased after the law enforcement (11.3% versus 22.4%, $p < 0.001$) but not in patients aged 36 to 39 years (20.3% versus 24%, NS). Frozen-thawed embryo cycles allowed similar cumulative pregnancy rate (30.6%, NS). Taking into account all frozen embryos still to be transferred, SET period offers a better overall pregnancy rate than the DET period (36.1% versus 32.3%, $p < 0.01$).

Capsule Belgian mandatory SET policy induced a dramatic reduction of twin deliveries. Cryopreservation allows the maintenance of a similar cumulative pregnancy rate.

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Conclusions The Belgian law allowed a dramatic reduction of twin deliveries especially for patients under 36 years. Cryopreservation maintains a similar cumulative pregnancy rate.

Keywords Single embryo transfer · Twin pregnancies · Cryopreservation

Introduction

Reducing multiple pregnancies in IVF due to obstetrical risks, prenatal and postnatal complications and the risk of long term sequels is certainly a public health priority [1–3].

Often couples wish for a twin pregnancy in order “to gain time” and to avoid having to start a cycle all over again [4]. But when these couples are properly informed of the risks associated with multiple pregnancy, the rate of those wishing single embryo transfer increases from 33% to 60% [5].

The objective therefore, is to limit multiple pregnancies while maintaining high delivery rates, and there is growing evidence in literature in favour of elective single embryo transfer policy.

A number of studies [6–13] have been carried out, namely in Finland and Belgium at the beginning of 2000 on single-embryo transfer. These studies showed that an excellent pregnancy rate could be obtained with a drastic decrease in twin pregnancy, although the selection based on patient's age (young patients <36 years of age), cycle rank as well as embryo morphology could have influenced the results favourably.

Randomised [7, 14] or retrospective [6, 15, 16] studies have later showed that elective single embryo transfer on a

fresh cycle, followed by one or more frozen-thawed embryo transfer cycles could allow for an overall pregnancy rate per ovarian puncture as high as 50% whilst still reducing multiple pregnancies.

Belgium introduced a new law which was applied on 1st July 2003 regulating the total number of transferred embryos.

In Fresh cycles:

- Age <35 years: at the 1st attempt single embryo transfer. At the 2nd attempt: single embryo transfer or double embryo transfer if embryo quality insufficient. Beyond 3rd attempt: double embryo transfer maximum.
- 35 years <age <40 years: at the 1st and 2nd attempt: double embryo transfer maximum. Beyond 3rd attempt: triple embryo transfer maximum.
- 39 years <age <43 years: no limitation in number of transferred embryos

In frozen-thawed cycles: double embryo transfer maximum.

Embryo transfer policy and limitation of ovarian stimulation were negotiated between the ministry of Health and Assisted Reproduction specialists with the aim of reducing the twin pregnancy ratio by 50%. Money saved this way on neonatal intensive care and by additional measures on drugs, permit the national insurance system to reimburse laboratory fees with up to 6 FIV-ICSI cycles for patients up to 43 years of age.

This study investigates the impact of the new transfer policy on patient outcome, analysing the database at Erasme hospital including data on fresh cycles followed by frozen-thawed cycles. Results are compared to a control group of patients who had treatment just before the application of the new law. Overall pregnancy and birth rates were compared as well as the role of cryopreservation on global success rate.

Materials and methods

Analysis is based on cycles performed between 01/07/2003 (date of new law enforcement) and 31/10/2008 (SET period), among whom the majority of transfers were single-embryo transfer (52%). Results were compared to a control group of cycles performed before the law application between 01/01/2001 and 30/06/2003 (DET period), where a majority of transfer involved the transfer of 2 embryos (58%). The control group selection (DET period) was intentionally limited to 01/01/2001, with the aim of having better homogeneity between the 2 groups and therefore minimizing biases influencing pregnancy rate (stimulation schemas, culture media, cryopreservation methods, etc...). The significant change during the studied

period was the introduction by law of a limit in the mean number of gonadotropins units reimbursed per cycle (2500 IU). This study includes all cycles of fresh embryo transfer after IVF (in vitro fertilisation) or ICSI (intracytoplasmic sperm injection), excluding only those who underwent oocyte donation, Preimplantation Genetic Diagnosis or carriers of viral diseases (HIV, hepatitis B or C). Data analysis is based on fresh cycle results as well as the subsequent frozen-thawed cycles if embryos were frozen during the fresh cycle. Data analysis was carried out on the global population treated in our clinic (maternal age 18–43 years) and on sub-groups based on age groups according to law (< 36 years, 36–39 years). For patients aged 40–43 years results are similar and are not presented, since the law has not changed practice in this age group.

Ovarian stimulation and puncture, laboratory techniques and embryo transfer protocols have been described previously [17]. Oocytes fertilization was realized with classic IVF (25%), ICSI (65%) or mixed (5%) in the two periods. Embryo transfer policy followed the Belgian law.

Embryo quality was assessed with a score [18] based on morphology including cleavage rate, absence of cytoplasmic fragments and blastomere regularity. Supernumerary embryos obtained in fresh cycles were frozen according to embryo morphology. The majority of embryos are frozen at the cleaved stage (5% PN2, 75% cleaved and 15% blastocysts). Frozen-thawed embryos were transferred at the same phase in development in which they were frozen and only if at least half of blastomeres were intact after thawing and if the embryo had undergone at least one cell division after 18 h in culture.

A pregnancy is defined as the presence of a gestational sac (GS) at ultrasound. Implantation rate is defined by the number of GS on the total number of transferred embryos. Pregnancy rate is defined as the ratio between the number of pregnancies and the number of transfer cycles. Twin pregnancies and triple pregnancies are defined by the presence of 2 or 3 GS at ultrasound. The multiple pregnancy rate is the number of multiple pregnancies over the total number of pregnancies.

Cumulative pregnancy and birth rates represent the addition of the number of pregnancies and births obtained after fresh embryo and frozen-thawed embryo transfers which belonged to the same oocyte puncture. Maximal pregnancy and birth rates are calculated taking into account potential pregnancies that could be obtained if all cryopreserved embryos were transferred since a certain number of frozen embryos are still cryopreserved.

Potential pregnancy and birth rates per thawed embryo were determined considering embryos that do not resist the thawing process. The number of potential pregnancies that could be obtained from frozen embryos stored in the bank is defined as the number of frozen stored embryos times

pregnancy and birth rate per thawed embryo. Maximal pregnancy and birth rates are therefore the addition of cumulative pregnancy and birth rates to potential pregnancy and birth rates.

Statistical analysis

Quantitative variables were summed up by their means $\pm$ standard deviation. Differences between continuous variables were assessed with *t*-test for independent samples or Wilcoxon rank-sum (Mann–Whitney U) test. Chi-square test or Fisher's exact probability with Yates correction were used to compare qualitative variables. Chi-square test or Fisher's exact probability with Yates correction were used to compare categorical variables. Analysis was completed using Statistical Package for the Social Sciences (SPSS) 18.0 for Windows XP (Microsoft Inc., Redmond, WA, USA). Only significant differences are presented in the results.

Results

Global results

A total of, 4122 cycles were carried out with fresh embryo transfer, followed by 1293 frozen-thawed cycles during the SET period. 2104 cycles with fresh embryo transfer followed by 609 frozen-thawed cycles were performed during the DET period.

Maternal age was slightly higher in SET period (35 versus 34 years, SET versus DET, respectively, $p < 0.001$) (Table 1).

Ovarian stimulation was less intense on SET period. The maximum oestradiol levels, number of IU of gonadotropins, number of collected oocytes and number of total embryos obtained were significantly lower in SET compared to DET period. The mean embryo score was slightly higher in SET period (Table 1).

Number of cycles with at least one frozen embryo, number of frozen embryos and mean frozen embryo score are all significantly higher in SET period (Table 1).

Table 1 Cycles characteristics

	SET period	DET period	P
Age from 18 to 43 years			
Number of cycles	4122	2104	
Age (years)	35 $\pm$ 5	34 $\pm$ 5	<0.001
Maximum Estradiol level (pg/ml)	2723 $\pm$ 1472	2818 $\pm$ 1452	<0.001
Gonadotropins units used per cycle (UI/ml)	2562 $\pm$ 1178	3048 $\pm$ 1490	<0.02
Number of oocytes picked-up (mean/cycle)	33059 (8 $\pm$ 4.8)	21467 (10.2 $\pm$ 5.2)	<0.001
Total number of embryos obtained (mean/cycle)	20019 (4.8 $\pm$ 3.2)	13252 (6.1 $\pm$ 3.9)	<0.001
Mean embryo score	3.8 $\pm$ 1.4	3.4 $\pm$ 1.4	<0.001
Number of transferred embryos (mean/cycle)	6553 (1.6 $\pm$ 0.7)	4609 (2.2 $\pm$ 0.6)	<0.001
Mean score of transferred embryos	4.5 $\pm$ 1.1	4.1 $\pm$ 1.1	<0.001
Number of cycles with cryopreservation	1849 (44.8%)	759 (36%)	<0.001
Number of frozen embryos	6656 (49.4%)	3053 (35.3%)	<0.001
Mean score of frozen embryos	4.4 $\pm$ 0.9	4.1 $\pm$ 0.7	<0.001
Age <36 years			
Number of cycles	2295	1370	
Number of transferred embryos (mean/cycle)	2890 (1.2 $\pm$ 0.4)	2876 (2.1 $\pm$ 0.5)	<0.01
Mean score of transferred embryos	4.7 $\pm$ 1.1	4.2 $\pm$ 1.0	<0.001
Number of cycles with cryopreservation	1362 (59.3%)	592 (43.2%)	<0.001
Number of frozen embryos	5160 (52%)	2430 (37.1%)	<0.001
Mean score of frozen embryos	4.4 $\pm$ 0.8	4.1 $\pm$ 0.7	<0.001
36 < age < 39 years			
Number of cycles	1044	487	
Number of transferred embryos (mean/cycle)	1931 (1.8 $\pm$ 0.6)	1161 (2.3 $\pm$ 0.7)	<0.001
Mean score of transferred embryos	4.3 $\pm$ 1.1	3.9 $\pm$ 1.1	<0.001
Number of cycles with cryopreservation	349 (33.4%)	136 (28%)	0.03
Number of frozen embryos	1122 (46.3%)	534 (33%)	<0.01
Mean score of frozen embryos	4.2 $\pm$ 0.9	4.1 $\pm$ 0.8	NS

The proportion of single embryo transfer has increased significantly in fresh cycles after the application of the new law (52% versus 11.7%, SET versus DET, respectively, $p < 0.001$). Pregnancy and birth rates were similar for the two periods while twin pregnancy and twin birth rates were significantly decreased in SET period (Table 2).

Pregnancy and birth rates after transfer of frozen-thawed embryos were higher in SET period ($p < 0.01$), although twin pregnancy rates remained similar because of identical proportion of double transfers between the two periods (Table 2). Therefore overall twin birth rate was still high for SET period (12.2%, Table 2). Cumulative pregnancy and birth rates (including fresh and frozen-thawed cycles) after thawing of only a part of frozen embryos (52.7% in SET period and 71.6% in DET period) are not significantly different in the two periods, but maximal pregnancy and

birth rates which would be achieved after thawing of all frozen embryos are higher in SET period (Table 2).

Age group results

Patients aged 20–35 years

Results are represented in Tables 1 and 3.

A significant decrease in twin pregnancies and twin births without a reduction in the overall pregnancy and birth rates was observed. One triplet birth has been observed in SET period, as a result of a double embryo transfer.

The SET period allowed the freezing of significantly more embryos resulting in a higher number of transfers per thawed embryo

Table 2 Results: global population (age 18 to 43 years)

Cycles number according to the number of transferred embryos	SET period			DET period				<i>P</i> <0.001
	1	2	3	1	2	3	4	
	2146 (52%)	1521 (37%)	455 (11%)	246 (11.7%)	1220 (58%)	629 (29.8%)	9 (0.5%)	
Fresh cycles								
Implantation rate	23.1%			19.8%				<0.001
Pregnancies	1308 (31.7%)			702 (33.3%)				NS
Twin pregnancies	186 (14.2%)			208 (29.6%)				<0.001
Deliveries	1011 (24.5%)			552 (26.2%)				NS
Twin deliveries	114 (11.3%)			124 (22.4%)				<0.001
Triplet deliveries	2 (0.1%)			4 (0.7%)				NS
Frozen-thawed cycles								
Number of thawed embryos	3509 (52.7%)			2188 (71.6%)				
Rate of surviving embryos at thawing	54.4%			42%				<0.001
Number of cycles with transfer	609			1293				
Number of transferred embryos (mean/cycle)	1911 (1.1±0.8)			921 (1.0±0.8)				NS
Implantation rate	18.3%			13.7%				<0.01
Pregnancies	309 (23.8%)			114 (18.7%)				0.01
Twin pregnancies	39 (12.6%)			12 (10.5%)				NS
Deliveries	253 (19.5%)			93 (15.2%)				0.02
Twin deliveries	27 (10.6%)			7 (7.5%)				NS
Cumulative pregnancies and deliveries								
Cumulative pregnancies	1617 (39.2%)			816 (38.7%)				NS
Cumulative twin pregnancies	225 (13.9%)			220 (27%)				<0.001
Cumulative deliveries	1264 (30.6%)			645 (30.6%)				<0.01
Cumulative twin deliveries	141 (12.2%)			131 (25.3%)				<0.001
Maximal pregnancies and deliveries								
Number of embryos still frozen	3147 (47.2%)			865 (28%)				
Pregnancy rate per thawed embryo	8.8%			5.2%				
Maximal pregnancies	1894 (45.9%)			861 (40.9%)				<0.001
Delivery rate per thawed embryo	7.3%			4.2%				
Maximal deliveries	1490 (36.1%)			681 (32.3%)				<0.01

Table 3 Results: age≤36 years

Cycles number according to the number of transferred embryos	SET period			DET period				<i>P</i> <0.01
	1	2	3	1	2	3	4	
	1703 (74.2%)	592 (25.7%)	1 (0.1%)	138 (10%)	966 (70.5%)	258 (18.8%)	8 (0.7%)	
Fresh cycles								
Implantation rate	32.3%			23.9%				<0.001
Pregnancies	846 (36.8%)			514 (37.5%)				NS
Twin pregnancies	88 (8.3%)			159 (25.2%)				<0.001
Deliveries	691 (30%)			427 (31.1%)				NS
Twin deliveries	58 (8.3%)			96 (22.4%)				<0.001
Triplet deliveries	1			3 (0.7%)				NS
Frozen-thawed cycles								
Number of thawed embryos	2630 (50.9%)			1732 (71.2%)				
Rate of embryos surviving at thawing	53.5%			42.8%				<0.01
Number of cycles with transfer	494			952				
Number of transferred embryos (mean/cycle)	1408 (1.5±0.5)			742 (1.5±0.6)				NS
Implantation rate	21%			14.5%				<0.001
Pregnancies	258 (27.1%)			96 (19.4%)				<0.001
Twin pregnancies	36 (13.9%)			12 (12.5%)				NS
Deliveries	222 (23.3%)			80 (16.1%)				<0.001
Twin deliveries	25 (11.2%)			7 (8.7%)				NS
Cumulative pregnancies and deliveries								
Cumulative pregnancies	1104 (48.1%)			610 (44.5%)				0.03
Cumulative twin pregnancies	124 (11.2%)			171 (28%)				<0.001
Cumulative deliveries	913 (39.7%)			507 (37%)				NS
Cumulative twin deliveries	83 (9%)			103 (20.3%)				<0.001
Maximal pregnancies and deliveries								
Number of embryos still frozen	2530 (49%)			698 (28.7%)				
Pregnancy rate per thawed embryo	9.8%			5.5%				
Maximal pregnancies	1351 (58.8%)			648 (47.3%)				<0.001
Delivery rate per thawed embryo	8.4%			4.6%				
Maximal deliveries	1133 (49.4%)			539 (39.3%)				<0.001

Pregnancy and birth rates, in frozen-thawed embryo cycles, were higher for the SET period ($p<0.01$). Twin pregnancy rate in frozen thawed cycles was however unchanged. Since cryopreservation of more than one good quality embryo per patient was achieved for SET period it was possible to obtain, after thawing a part of the frozen embryos (50.9% in SET versus 71.2% in DET period respectively) a higher cumulative pregnancy rate in SET with a 50% less twin pregnancy rate compared to DET.

After thawing all frozen embryos, SET pregnancy and birth rates would be significantly higher compared to DET.

Patients aged 36–39 years

Results are represented in Tables 1 and 4.

Pregnancy and birth rates were similar for the two periods, even though the SET mean number of transferred embryos was significantly lower. Twin pregnancy and birth rates stayed identical between for SET and DET in this age group.

Number of cycles with cryopreservation and number of frozen embryos were higher for SET period. Mean frozen embryos score is similar.

In frozen-thawed embryos cycles, pregnancy and birth rates as well as the twin birth rate were similar for SET and DET periods.

Cumulative pregnancy and birth rates after thawing of a part of frozen embryos (56.7% in SET period and 71.1% in DET period) were not statistically different. The transfer of the residual frozen embryos would not achieve a significant higher maximal pregnancy and birth rates.

Table 4 Results: age 36 to 39 years

Cycles number according to the number of transferred embryos	SET period			DET period				<i>P</i> <0.001
	1	2	3	1	2	3	4	
	248 (23.7%)	705 (67.5%)	91 (8.8%)	61 (12.5%)	179 (36.7%)	246 (50.5%)	1 (0.3%)	
Fresh cycles								
Implantation rate	21%			16.2%				<0.001
Pregnancies	327 (31.3%)			137 (28.1%)				NS
Twin pregnancies	76 (18.7%)			40 (21.3%)				NS
Deliveries	241 (23%)			100 (20.5%)				NS
Twin deliveries	49 (20.3%)			24 (24%)				NS
Frozen-thawed cycles								
Number of thawed embryos	637 (56.7%)			380 (71.1%)				
Rate of embryos surviving at thawing	57.6%			39.2%				<0.001
Number of cycles with transfer	248			95				
Number of transferred embryos (mean/cycle)	367 (1.5±0.5)			149 (1.6±0.6)				NS
Implantation rate	11.9%			11.4%				NS
Pregnancies	42 (16.9%)			17 (17.8%)				NS
Twin pregnancies	2 (4.7%)			0				NS
Deliveries	25 (10%)			11 (11.5%)				NS
Twin deliveries	1			0				
Cumulative pregnancies and deliveries								
Cumulative pregnancies	369 (35.3%)			154 (31.6%)				NS
Cumulative twin pregnancies	78 (21.1%)			40 (26%)				NS
Cumulative deliveries	266 (25.4%)			111 (22.8%)				NS
Cumulative twin deliveries	50 (18.7%)			24 (21.6%)				NS
Maximal pregnancies and deliveries								
Number of embryos still frozen	485			154				
Pregnancy rate per thawed embryo	6.6%			4.5%				
Maximal pregnancies	401 (38.4%)			161 (33%)				0.05
Delivery rate per thawed embryo	3.5%			2.9%				
Maximal deliveries	285 (27.2%)			115 (23.6%)				NS

Discussion

Since application of the new transfer policy on the 01/07/2003, twin pregnancies have been reduced by half (11.3% versus 22.4%, in SET and DET, respectively, $p<0.001$) without a decrease in pregnancy and birth rates, even if maternal age is slightly higher for the SET period.

The limitation by law of the number of gonadotropins units reimbursed per cycle (2500 IU) explain the less intense ovarian stimulation in the SET period demonstrating lower maximum oestradiol levels, number of IU of gonadotropins, number of collected oocytes and number of total embryos obtained.

The Belgian transfer policy now permits less fresh embryos to be transferred at the same time and has resulted in an increase in the number and quality of frozen embryos, therefore increasing the SET number of frozen-thawed

cycles. Overall pregnancy and birth rates are similar in the two periods (39.2% versus 38.7% and 30.6% versus 30.6%, SET and DET period, respectively, NS). Transfer of all frozen embryos could allow maximal pregnancy and birth rates to be higher in SET period.

Law maximal impact is seen in patients under 36 years of age where 74% of transfers are SET. This has not had any impact on the pregnancy rate in that age group (36.8% versus 37.5%, in SET and DET periods, NS) but has significantly decreased twin birth rate (8.3% versus 22.4%, respectively, $p<0.001$). Residual twin births in this age group are a result of transfers beyond first attempt (32.7% and 36.2% of twin births occur respectively from 2nd and 3rd line of treatment). Extension of single embryo transfer beyond first attempt in this age group should be considered.

Flexibility of Belgian law on embryo transfer, where the number of transferred embryos depends on patient charac-

teristics, is probably responsible for the low impact on the reduction of twin pregnancies beyond 36 years. The application of the new law has thus moved the peak of twin pregnancies towards patients aged of 36 to 39 years. This group age contributes most to residual twin pregnancies (76 out of 114, 66.7%).

Efforts to diminish twin pregnancies need to be applied to patients aged 36 to 39 years. A retrospective study [19] shows that elective single embryo transfer could lead to a higher cumulative pregnancy rate (41.8% versus 26%, $p < 0.0001$) than the 2 embryo transfer group. Overall multiple pregnancy rate (1.7% versus 16.6%, $p < 0.0001$) was significantly lower in the single embryo group.

As far as frozen-thawed cycles are concerned, Belgian law authorizes 2 embryos to be transferred from first attempt. Therefore overall multiple birth rates continue to be high (12.2%, Table 2). Single embryo transfer up until 38 years of age in frozen-thawed cycles would result in the disappearance of multiple pregnancies in those cycles (38 multiple pregnancies) without any negative impact on pregnancy rate.

Randomised studies [7, 14, 20–22] comparing 1 or 2 embryo transfer on a population at risk of multiple pregnancies (maternal age < 36 or 34 years, number of high quality embryos) shows a decrease of pregnancy rate in fresh cycles. Therefore thawing frozen embryos allows the re-establishing of pregnancy rate which was otherwise decreased. Single embryo transfer is recommended in this high risk group.

Recent retrospective studies [16, 23] shows that elective single embryo transfer after replacement of thawed embryos results in similar pregnancy rates and a significant decrease in multiple pregnancy rates.

A randomised study [24] compared in a non selected population (first cycle, regardless of age), single versus two embryos transfer in fresh cycles. A 50% decrease of ongoing pregnancies (21.4% versus 40.3%, $p < 0.05$) with a virtual disappearance of multiple pregnancies (0% versus 21%, $p < 0.05$) was observed. If thawed embryos are taken into consideration overall ongoing pregnancy ratio stays lower in single embryo transfer group (29.9% versus 42.2%, $p < 0.01$). Meanwhile, single embryo transfer in a selected group (age < 38 years, at least one good quality embryo) enables a clinical pregnancy rate per transfer of 31.5% with a multiple pregnancy ratio of 12.5%.

A recent meta-analysis [25] concludes that elective single embryo transfer results in a higher chance of delivering a term singleton live birth compared with double embryo transfer. As previously reported, elective SET yields a lower live birth rate than DET, but this difference is almost completely overcome by an additional fresh or frozen single embryo transfer cycle.

In conclusion, Belgian policy obtained its objectives without diminishing overall pregnancy rate. Increase in

number of frozen embryos, after thawing and transfer, allows for high pregnancy and delivery rates. Therefore efforts could be still made in order to obtain an additional decrease of multiple pregnancy rates. Attention should be focused on patients of 36 years of age or more and on the replacement of thawed embryos. Progress in cryopreservation technique such as vitrification could increase pregnancy rate after thawing. In this case professionals should extend single thawed embryo transfer policy therefore decreasing multiple pregnancy rates. Patients and practitioners would more easily accept single embryo transfer if they were convinced that the global success rate would either not be affected, or only very slightly, despite a significant additional decrease of multiple pregnancies.

References

1. ESHRE Capri Workshop Group. Multiple gestation pregnancy. *Hum Reprod.* 2000;15(8):1856–64.
2. Andersen AN, Goossens V, Ferraretti AP, Bhattacharya S, Felberbaum R, de Mouzon J, et al. Assisted reproductive technology in Europe, 2004: results generated from European registers by ESHRE. *Hum Reprod.* 2008;23:756–71.
3. Land JA, Evers JL. Risks and complications in assisted reproduction techniques: report of an ESHRE consensus meeting. *Hum Reprod.* 2003;18:455–45.
4. Laruelle C, Englert Y. Psychological study of in vitro fertilization-embryo transfer participants' attitudes toward the destiny of their supernumerary embryos. *Fertil Steril.* 1995;63:1047–50.
5. Newton CR, Mc Bride J, Feyles V, Tekpetey F, Power S. Factors affecting patients's attitudes toward single and multiple-embryo transfer. *Fertil Steril.* 2007;87:269–78.
6. Vilska S, Tiitinen A, Hyden-Granskog C, Hovatta O. Elective transfer of one embryo results in an acceptable pregnancy rate and eliminates the risk of multiple birth. *Hum Reprod.* 1999;14:2392–5.
7. Gerris J, De Neubourg D, Mangelschots K, Van Royen E. Prevention of twin pregnancy after in IVF or ICSI based on strict embryo criteria: a prospective randomized clinical trial. *Hum Reprod.* 1999;14:2581–7.
8. Dhont M. Single embryo transfer. *Semin Reprod Med.* 2001;19:251–8.
9. Surrey E, Gardner DK, Stevens J, Minjarez D, Leitz A, Schoolcraft WB. Single blastocyst stage after in vitro fertilization (IVF): a prospective randomized trial. *Fertil Steril.* 2002;78 Suppl 1:S42.
10. Gerris J, De Neubourg D, Mangelschots K, Van Royen E, Vercuyssens M, Barudy-Vasquez J. Elective single day 3 embryo transfer halves the twinning rate without decrease in the ongoing pregnancy rate of an IVF/ICSI programme. *Hum Reprod.* 2002;17:2626–31.
11. Marek D, Langley M, Nackley AC, Doody KM, Doody KJ. Elective single embryo transfer in fresh cycles. *Fertil Steril.* 2002;78 Suppl 1:S48.
12. Marek D, Langley M, Nackley AC, Doody KM, Doody KJ. Frozen embryo transfer of single blastocysts. *Fertil Steril.* 2002;78 Suppl 1:S132.
13. Kovacs G, MacLachlan V, Rombauts L, Healy D, Howlett D. Replacement of one selected embryo is just as successful as two embryo transfer, without the risk of twin pregnancy. *Aust N Z J Obstet Gynaecol.* 2003;43:369–71.

14. Martikainen H, Tiitinen A, Tomas C, et al. One versus two embryo transfer after IVF and ICSI: a randomised study. *Hum Reprod.* 2001;16:1900–3.
15. Tiitinen A, Haltunen M, Harkki P. Elective single-embryo transfer: the value of cryopreservation. *Human Reprod.* 2001;16:1140–4.
16. Veleva Z, Karinen P, Tomas C, Tapanainen J, Martikainen H. Elective single embryo transfer with cryopreservation improves the outcome and diminishes the costs of IVF/ICSI. *Human Reprod.* 2009;24:1632–9.
17. Devreker F, Emiliani S, Revelard Ph, Van den Bergh M, Govaerts I, Englert Y. Comparison of two elective transfer policies of two embryos to reduce multiple pregnancies without impairing pregnancy rates. *Human Reprod.* 1999;14:83–9.
18. Puissant F, Van Rysselberge M, Barlow P, Deweze J, Leroy F. Embryo scoring as a prognostic tool in IVF treatment. *Hum Reprod.* 1987;2:705–8.
19. Veleva Z, Vilska S, Hyden-granskog C, Tiitinen A, Tapanainen JS, Martikainen H. Elective single embryo transfer in women aged 36–39 years. *Hum Reprod.* 2006;21:2098–102.
20. Thurin A, Hausken J, Hillensjo T, Jablonowska B, et al. Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization. *N Engl J med.* 2004;351:2392–402.
21. Gardner DK, Surrey E, Minjarez D, Leitz A, Stevens J, Schoolcraft WB. Single blastocyst transfer: a prospective randomized trial. *Fertile Steril.* 2004;81:551–5.
22. Lukassen HG, Braat DD, Wetzels AM, Zielhuis GA, Adang EM, Scheenjes E, et al. Two cycles with Single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial. *Hum Reprod.* 2005;20:702–8.
23. Roberts SA, McGowan L, Mark Hirst W, Vail A, Rutherford A, Lieberman BA, et al. The toward SET collaboration. Reducing the incidence of twins from IVF treatments: predictive modelling from a retrospective cohort. *Hum Reprod.* 2011;26(3):569–75.
24. Van Montfoort AP, Fiddelers AA, Janssen JM, Derhaag JG, Dirksen CD, Dunselman GA, et al. In unselected patients, elective single embryo transfer prevents all multiples, but Results in significantly lower pregnancy rates compared with double embryo transfer: a randomized controlled trial. *Hum Reprod.* 2006;21:338–43.
25. McLernon DJ, Harrild K, Bergh C, Davies MJ, de Neubourg D, Dumoulin JC, et al. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. *BMJ.* 2010;341:6945.