Perinatal outcomes after assisted reproductive technology treatment in Australia and New Zealand: single versus double embryo transfer

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ABSTRACT

Objective: To compare the perinatal outcomes of babies conceived by single embryo transfer (SET) with those conceived by double embryo transfer (DET).

Design, setting and participants: A retrospective population-based study of embryo transfer cycles in Australia and New Zealand between 2002 and 2006, using data from the Australia and New Zealand Assisted Reproduction Database.

Main outcome measures: Proportion of SET procedures; comparison of SET and DET procedures with respect to multiple births, low birthweight (LBW), preterm birth and fetal death.

Results: The proportion of SET procedures has increased from 28.4% in 2002 to 32.0% in 2003, 40.5% in 2004, 48.2% in 2005 and 56.9% in 2006. The multiple birth rate for all babies conceived by SET (4.0%) was 10 times lower than for those conceived by DET (39.1%) ($P < 0.01$). The average birthweight for all liveborn babies conceived by SET (3290 g) was higher than for those conceived by DET (2934 g) ($P < 0.01$). The preterm birth rate of all DET-conceived babies (30.3%) was higher than for SET-conceived babies (12.3%) (adjusted odds ratio [AOR], 3.19 [95% CI, 3.01–3.38]). All babies conceived by DET were more likely to be stillborn than those conceived by SET (AOR, 1.49 [95% CI, 1.21–1.82]). Singletons conceived by DET were more likely to be born preterm than singletons conceived by SET (AOR, 1.13 [95% CI, 1.05–1.22]). Liveborn singletons conceived by DET were 15% more likely to have LBW than liveborn singletons conceived by SET (AOR, 1.15 [95% CI, 1.05–1.26]). There was no significant difference in fetal death rate between DET- and SET-conceived singletons.

Conclusion: The increase in proportion of SET procedures has resulted in a lower rate of multiple births and in better perinatal outcomes in Australian and New Zealand assisted reproduction programs.

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Since 2002, the Reproductive Technology Accreditation Committee in Australia and New Zealand has advocated reducing the number of embryos transferred to women undergoing assisted reproductive technology (ART) treatment, with the aim of minimising the number of multiple births.[1] Studies suggest that the high incidence of multiple births following ART is responsible for most adverse perinatal outcomes (preterm birth, low birthweight [LBW] and perinatal death).[2-4]

The high rate of multiple births following ART is largely explained by the number of embryos transferred. Transferring two embryos (double embryo transfer [DET]) increases the odds of a multiple gestation by more than 60 times[5] compared with single embryo transfer (SET). Recent studies from Finland concluded that babies conceived by SET had better neonatal outcomes than those conceived after transferring two or more embryos.[6] This is the case even among singletons.[7,8] Belgium and the Scandinavian countries have endorsed SET as best practice, with Sweden reporting that SET is used in 70% of its embryo transfer cycles.[9]

The *Assisted reproduction technology in Australia and New Zealand 2006* report[10] showed that the proportion of embryo transfer cycles using SET had increased from 28.4% in 2002 to 56.9% in 2006 in Australia and New Zealand. Over the same period, the twin rate declined from 18.8% to 11.3%.

The aim of our study was to compare the perinatal outcomes of babies conceived by SET with those conceived by DET using data from the Australia and New Zealand Assisted Reproduction Database (ANZARD).

METHODS

Data source

ANZARD is housed at the Australian Institute of Health and Welfare (AIHW) National Perinatal Statistics Unit. Data from fertility centres in Australia and New Zealand, including information on each treatment cycle commenced, pregnancy and birth outcomes, are validated and entered into the database at the National Perinatal Statistics Unit. Data collection on pregnancy and neonatal outcomes varies between fertility centres but includes follow-up with the patient or clinician and the use of routine data from the relevant health department. Information on pregnancy outcomes and neonatal outcomes is missing for about 2% of clinical pregnancies recorded in ANZARD.

We carried out a retrospective analysis of ANZARD data on embryo transfer cycles and subsequent pregnancy and baby outcomes for the period 2002–2006.

Outcome measures and definition of terms

- *Maternal age.* Maternal age was expressed as the number of completed years at the time of ART treatment.
- *Type of embryo.* Embryos were classified as fresh (never frozen) or thawed (following cryopreservation).
- *Stage of embryo development.* Embryos were classified as cleavage-stage embryos or blastocysts.
- *Gestational age.* Defined as the number of completed weeks of gestation of the fetus, gestational age was calculated from the formula [(pregnancy end date minus embryo transfer date) plus 16 days].
- *Perinatal outcomes.* Outcomes examined were LBW (birthweight <2500 g in liveborn babies), preterm birth (gestational age <37 completed weeks) and fetal death (stillbirth) (number of fetal deaths per 1000 births).

Statistical analysis

The number and proportion of SETs and DETs were stratified by women's age (<35 years, 35–39 years or ⩾40 years) and described by year. SET and DET were compared with respect to perinatal outcomes for all babies,

with *t* tests used for continuous variables and χ^2 tests used for categorical variables. Univariate and multivariate logistic regression analyses were used to examine the likelihood of adverse perinatal outcomes. Data were analysed using SPSS software, version 16.0 (SPSS Inc, Chicago, Ill, USA).

Ethics approval

Our study was approved by the Human Research Ethics Committee of the University of New South Wales.

RESULTS

Number of embryos transferred

In Australia and New Zealand over the period 2002–2006, there were 172 190 cycles in which embryos were transferred: 73 563 SET cycles (42.7%), 93 429 DET cycles (54.3%) and 5198 cycles (3.0%) in which three or more embryos were transferred. Women aged 40 years or older tended to have a lower proportion of SETs compared with younger women.

The overall proportion of SETs increased from 28.4% in 2002 to 32.0% in 2003, 40.5% in 2004, 48.2% in 2005 and 56.9% in 2006. Between 2002 and 2006, the proportion of SETs increased from 28.7% to 66.2% for women aged < 35 years, from 27.5% to 54.4% for women aged 35–39 years, and from 29.1% to 42.5% for women aged ⩾ 40 years.

Perinatal outcomes

Over the period 2002–2006, 40 483 babies (73.0% singletons, 26.3% twins, 0.7% triplets or higher) were born to women who had either SET or DET cycles in Australia and New Zealand. Of these babies, 14 022 (34.6%) were conceived by SET and 26 461 (65.4%) by DET. The multiple birth rate for babies born to women who had SET cycles (4.0%) was about 10 times lower than for those born to women who had DET cycles (39.1%) ($P < 0.01$; $\chi^2 = 5768.3$; df = 1) (Box 1).

The overall preterm birth rate was 24.1%. The mean birthweight of liveborn babies was 3058 g, with 19.2% of babies having LBW. There were 520 fetal deaths (12.8 fetal deaths per 1000 births) after either SET or DET.

Type of embryo

Liveborn babies conceived after thawed embryo transfer cycles had a significantly lower rate of LBW than those conceived after fresh embryo transfer cycles, regardless of whether they were SET or DET. Similarly, the rate of preterm birth was significantly lower for babies conceived after thawed embryo transfer cycles than after fresh embryo transfer cycles. The fetal death rate was lower after thawed embryo transfer cycles than after fresh embryo transfer cycles for DET babies but not SET babies (Box 2).

Stage of embryo development

About 5% of babies conceived by single blastocyst transfer were multiples, which is significantly higher than the 3.4% for babies conceived by single cleavage-stage embryo transfer ($P < 0.01$). The multiple birth rate was 42.1% for babies conceived by double blastocyst transfer compared with 38.7% for babies conceived by double cleavage-stage embryo transfer ($P < 0.01$).

Babies conceived by blastocyst transfer had a significantly lower rate of LBW and

1 Number (%) of babies born to women following SET or DET procedures, Australia and New Zealand, 2002–2006

	SET	DET	Total
Singletons	13 468 (96.0%)	16 100 (60.9%)	29 568 (73.0%)
Multiples	554 (4.0%)	10 361 (39.1%)	10 915 (27.0%)
Twins	532 (3.8%)	10 090 (38.1%)	10 622 (26.3%)
Triplets or higher	22 (0.2%)	271 (1.0%)	293 (0.7%)

DET = double embryo transfer. SET = single embryo transfer. ◆

2 Perinatal outcomes of babies born following SET or DET procedures, by type of embryo, Australia and New Zealand, 2002–2006

Number and type of embryo	Total liveborn babies	Proportion of LBW liveborn babies	*P**	Total babies	Proportion of preterm births (all babies)	*P**	Fetal deaths/ 1000 births (all babies)	*P**
SET								
Fresh embryo	9 121	9.5%	< 0.01	9 229	12.9%	< 0.01	10.1	0.79
Thawed embryo	4 736	7.3%		4 793	11.2%		9.6	
DET								
Fresh embryo	18 402	27.7%	< 0.01	18 737	32.5%	< 0.01	16.1	< 0.01
Thawed embryo	7 620	17.7%		7 724	25.0%		10.4	
All								
Fresh embryo	27 523	21.7%	< 0.01	27 966	26.0%	< 0.01	14.1	< 0.01
Thawed embryo	12 356	13.7%		12 517	19.7%		10.1	

DET = double embryo transfer. LBW = low birthweight. SET = single embryo transfer. * χ^2 test, df = 1. ◆

3 Perinatal outcomes of babies born following SET or DET procedures, by stage of embryo development, Australia and New Zealand, 2002–2006

Number and stage of embryo development	Total liveborn babies	Proportion of LBW liveborn babies	*P**	Total babies	Proportion of preterm births (all babies)	*P**	Fetal deaths/ 1000 births (all babies)	*P**
SET								
Cleavage stage	8 877	8.6%	0.61	8 971	12.0%	0.08	8.7	0.05
Blastocyst	4 980	8.9%		5 051	13.0%		12.1	
DET								
Cleavage stage	22 083	24.9%	0.55	22 447	30.4%	0.36	14.3	0.64
Blastocyst	3 939	24.3%		4 014	29.7%		15.2	
All								
Cleavage stage	30 960	20.2%	< 0.01	31 418	25.1%	< 0.01	12.7	0.55
Blastocyst	8 919	15.7%		9 065	20.4%		13.5	

DET = double embryo transfer. LBW = low birthweight. SET = single embryo transfer. * χ^2 test, df = 1. ◆

preterm birth than those conceived by cleavage-stage embryo transfer. Babies conceived by single blastocyst transfer had slightly higher rates of preterm birth and fetal death than those conceived by single cleavage-stage embryo transfer. The fetal death rate was 15.2 per 1000 births for babies after double blastocyst transfer cycles, compared with 14.3 per 1000 births for babies after double cleavage-stage embryo transfer cycles, but the difference between the two was not significant (Box 3).

Birthweight

The mean birthweight for all liveborn babies conceived by SET (3290 g) was significantly higher than the mean for those conceived by DET (2934 g) ($P < 0.01$). Term liveborn singletons conceived by SET had significantly higher mean birthweight (3430 g) than those conceived by DET (3401 g), regardless of sex ($P < 0.01$). There was no significant difference between SET- and DET-conceived babies in mean birthweight of liveborn singletons born at 32–36 weeks of gestation (Box 4).

Liveborn babies conceived by DET were 3.6 times more likely to have LBW than those conceived by SET (Box 5). Liveborn singletons conceived by DET had a significantly lower mean birthweight (3287 g) than singletons conceived by SET (3332 g) ($P < 0.01$). Consistent with this, liveborn singletons conceived by DET were 15% more likely to have LBW than singletons conceived by SET (adjusted odds ratio [AOR], 1.15 [95% CI, 1.05–1.26]) (Box 5).

Preterm birth

The preterm birth rate of all babies conceived by DET was 30.3%, compared with a rate of 12.3% for babies conceived by SET. Singletons conceived by DET were 13% more likely to be born preterm than those conceived by SET (Box 5).

Fetal death

Babies conceived by DET were more likely to be stillborn than those conceived by SET (AOR, 1.49 [95% CI, 1.21–1.82]). The fetal death rate for singletons conceived by DET (10.9 deaths/1000 births) was slightly higher than the rate for singletons conceived by SET (8.6 deaths/1000 births), but the difference was not significant (Box 5).

Perinatal outcomes of multiples

Unlike singletons, multiples conceived by DET had better perinatal outcomes than those conceived by SET (Box 5). However, more than half of liveborn multiples (whether conceived by DET or SET) were LBW and 60% of multiples were born preterm.

DISCUSSION

Consistent with other studies,[6,8,11] we found that babies conceived by SET had better perinatal outcomes than those conceived by DET. This was the case even for singletons. Regardless of maternal age, DET-conceived singletons had 15% greater odds of LBW and 13% greater odds of preterm birth than SET-conceived singletons.

Our analysis showed that the multiple birth rate for babies conceived by DET was nearly 10-fold higher than for babies conceived by SET. Multiple births are strongly associated with poorer perinatal outcomes.[4,12] LBW and preterm birth have been shown to be directly related to fetal and neonatal death, and short- and long-term morbidity and mortality.[13,14]

The rationale for favouring DET over SET, until recently, has been that the transfer of two or more embryos results in a higher clinical pregnancy rate than the transfer of only one embryo, especially in younger women.[15] However, a higher clinical pregnancy rate does not mean better perinatal outcomes for the baby.

Multiple gestations not only increase the risk for babies, but also for mothers.[16,17] Threatened miscarriage, hyperemesis, thromboembolism, hypertension, haemorrhage and maternal mortality are all significantly increased in multiple gestations.[17] There is also a greater risk of depression and marital decline after multiple gestations.[16]

In addition, multiple gestations place a greater economic and social burden on the parents and on the health care system.[18,19] In Australia in 2003, the average combined cost of infant and maternal birth admission following ART treatment was $8053 for singletons compared with $23 214 for twins and $90 742 for higher-order multiples.[20]

One of the findings of our study was that preterm birth and LBW were less likely to occur in babies conceived by thawed embryo transfer than fresh embryo transfer. This is consistent with other studies[3,21] showing that cryopreservation does not adversely affect fetal development or perinatal outcomes, but in fact appears to have a protective effect. The better outcomes of babies conceived from frozen embryos are likely to be related to the more similar ovarian and uterine conditions in thawed embryo transfer cycles to those for non-ART conceptions.[21]

Twins conceived by SET are considered to be monozygotic twins.[22] In general, monozygotic twins have worse perinatal outcomes than dizygotic twins.[23] Consistent with other studies,[22] our data showed a significantly higher rate of twins following blastocyst transfer (both SET and DET) than cleavage-stage embryo transfer. But overall outcomes were more favourable for babies following blastocyst transfer than cleavage-stage embryo transfer. This may largely be explained by more DET in cleavage-stage embryo transfer cycles than in blastocyst transfer cycles, and hence an overall higher multiple birth rate following cleavage-stage embryo transfer cycles. A significantly lower LBW rate was observed for singletons following blastocyst transfer in our study, which supports the suggestion that the blastocyst culture could have had an impact on higher birthweight.[24]

4 Mean birthweight of liveborn singletons following SET or DET procedures, by gestational age, Australia and New Zealand, 2002–2006

	SET		DET		
	Number of live births	Mean birthweight (g) (SD)	Number of live births	Mean birthweight (g) (SD)	*P**
Female singletons					
< 32 weeks	98	1483.3 (900.0)	146	1225.0 (757.1)	0.02
32–36 weeks	465	2559.4 (548.3)	614	2518.7 (574.3)	0.24
⩾ 37 weeks	5 835	3364.6 (467.7)	7 071	3333.1 (475.5)	< 0.01
Male singletons					
< 32 weeks	115	1367.3 (752.4)	168	1264.5 (703.3)	0.24
32–36 weeks	569	2631.7 (557.1)	721	2616.9 (560.6)	0.64
⩾ 37 weeks	6 117	3492.8 (485.3)	7 021	3469.3 (493.0)	0.01
All singletons					
< 32 weeks	214	1422.4 (822.1)	315	1247.1 (727.0)	0.01
32–36 weeks	1 034	2599.2 (554.0)	1 337	2571.6 (568.6)	0.24
⩾ 37 weeks	11 953	3430.2 (481.1)	14 105	3400.8 (489.2)	< 0.01

DET = double embryo transfer. SET = single embryo transfer. * *t* test. ◆

5 Perinatal outcomes of babies born following SET or DET procedures, Australia and New Zealand, 2002–2006

	SET	DET	OR (95% CI)	AOR* (95% CI)
All babies				
Low birthweight of liveborn babies	8.7%	24.8%	3.44 (3.23–3.68)	3.55 (3.32–3.80)
Preterm birth of all babies	12.3%	30.3%	3.10 (2.92–3.28)	3.19 (3.01–3.38)
Fetal death of all babies†	9.9%	14.4%	1.46 (1.20–1.77)	1.49 (1.21–1.82)
Singletons				
Low birthweight of liveborn singletons	6.6%	7.9%	1.21 (1.11–1.32)	1.15 (1.05–1.26)
Preterm birth of all singletons	10.1%	11.3%	1.14 (1.06–1.23)	1.13 (1.05–1.22)
Fetal death of all singletons†	8.6%	10.9%	1.27 (1.00–1.60)	1.26 (0.98–1.62)
Multiples				
Low birthweight of liveborn multiples	61.4%	51.2%	0.66 (0.55–0.79)	0.60 (0.50–0.72)
Preterm birth of all multiples	67.1%	59.8%	0.72 (0.60–0.87)	0.66 (0.55–0.80)
Fetal death of all multiples†	41.5%	19.9%	0.47 (0.30–0.73)	0.46 (0.29–0.73)

AOR = adjusted odds ratio. DET = double embryo transfer. OR = odds ratio. SET = single embryo transfer. * Adjusted for women's age, cause of infertility, parity, number of previous assisted reproductive technology treatments, type of embryo, and stage of embryo development. † Number of fetal deaths per 1000 births. ◆

Strengths of our study were the large study population and the two-nation coverage. One limitation was that elective embryo transfer procedures could not be distinguished from *all* embryo transfer procedures. (A Belgian study has shown that babies conceived by elective SET have better perinatal outcomes than those conceived by DET.[25]) Another limitation of our study was the potential variability in case reporting. The follow-up information on pregnancy and birth outcomes was collected in a number of ways, including follow-up by the treatment doctors and self-report by patients to fertility clinics. A further limitation was that data on the 2002–2006 study population were incomplete: information on pregnancy and birth outcomes was not stated for 1.7% of clinical pregnancies.

Our study confirms that the Reproductive Technology Accreditation Committee's policy of shifting towards greater use of SET in ART is working. In 2006, more than half of embryo transfer cycles were SETs, resulting in a fall in the multiple delivery rate to 12%, the lowest rate ever reported in Australia and New Zealand. Given the fewer maternal complications, lower rate of adverse perinatal outcomes and higher cost-effectiveness ratio for SET compared with DET, continuing to encourage SET will benefit women and their babies, as well as society in general.

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COMPETING INTERESTS

None identified.

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