Selective single blastocyst transfer reduces the multiple pregnancy rate and increases pregnancy rates: a pre- and postintervention study

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KEYWORDS
Blastocyst transfer ▪clinical pregnancy ▪IVF ▪multiple pregnancy ▪single embryo transfer pregnancy

ABSTRACT

Objective To examine the clinical pregnancy rate (CPR) and multiple pregnancy rate (MPR) in a large in vitro fertilisation (IVF) programme before and after the introduction of single blastocyst transfer (SBT) strategy in a selected group of women.

Design A 3-year pre- and postintervention study.

Setting A tertiary reproductive medicine and assisted conception unit in a London teaching hospital.

Population Two thousand four hundred and fifty-one fresh IVF cycles performed between July 2004 and June 2007 at the Assisted Conception Unit at Guy's and St Thomas' Hospital NHS Foundation Trust were included in the study.

Methods In January 2006, we implemented a multidisciplinary intervention involving the introduction of a selective day 5 SBT service together with an educational programme on the risks of multiple pregnancy and potential advantages of blastocyst transfer aimed at couples at high risk of multiple pregnancy.

Main outcome measures The CPR per cycle started and MPR per clinical pregnancy achieved.

Results A statistically significant increase in the CPR from 27% (324/1198) to 32% (395/1253) (risk difference [RD] 5%, risk ratio [RR] 1.17, 95% CI 1.03–1.32, P= 0.015) and reduction in the MPR per clinical pregnancy from 32% (103/272) to 17% (69/395) (RD 15%, RR 0.46, 95% CI 0.35–0.60, P < 0.001) were observed after introduction of the SBT service.

Conclusion Selective SBT in women with good prognosis can reduce the MPR after IVF while maintaining the overall success rate of the IVF programme.

How Do Iatrogenic Multiple Pregnancies Complicate Perinatal Care?

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The widespread availability of assisted conception has increased the numbers of multiple births. Iatrogenic multiple pregnancy now considered a complication of ART and IVF, creating complex and controversial problems (1), including increased frequency of fetal and maternal complications (2). These circumstances should prompt specialists not only to seek solutions to the problems with prenatal care, but also to decrease the numbers of IMP.

Is Plurality Directly Related To Birth Weight And Gestational Age?

The presence of more than one fetus may overwhelm the uterine capacity to adequately nurture multiple offspring (3), especially after IVF treatment (4). After IVF, the rate of extreme preterm births differs markedly between singleton, twin and triplet pregnancies (4). The rate of 20-27 week gestation for triplets (2.4%) is twice that of twins and 12 times higher than singletons. This difference is even more pronounced for the gestation period of 28-32 weeks, for which the rate for triplets (26%) is 3.9 times higher than for twins and 18.6 times higher for singletons. Moreover, the rates of newborns weighing <1,500 g were multiplied by 4.5 for twins and 20 for triplets compared to singletons. For babies with a weight <2,500 g these figures were 5 and 10, respectively and 2.5 and 3.5 for a small for gestational age babies (4). Data of Alexander et al (5) on spontaneous births also indicates the differences in the percentage of small for gestational age for singletons, twins and triplets. At week 34, 28% of all twins were SGA, at week 37, 40% and at week 39, 50%. For triplets, 50% were SGA at week 35 (5).

Is Plurality Directly Related To Adverse Fetal Risk?

Infants of multiple births are also at greater risk for neonatal morbidity and fetal, neonatal and post-neonatal mortality. Data of Papiernik and de Mouzon collected over a 14-year time span from a register of French IVF units shows very important increases in perinatal mortality rates for twins and triplets births compared to singletons births (4). These rates were multiplied by 2 to 4 in twins and by 4 to 8 in triplets, respectively. Finally, only 87.0% of triplets were considered healthy at the time of their birth compared to 98.1% for singletons. After discharge from the NICU, premature and low-birth-weight infants continue to experience

high rates of morbidity. Such infants are likely to require more intensive outpatient service and recurrent hospitalizations and are at risk for long-term handicap and disabilities (6).

Is Plurality Directly Related To Adverse Maternal Outcome?

Multiple pregnancy is accompanied by very serious implications for the mother in terms of hypertensive disorders, eclampsia, complications of treatment for premature contractions and prolonged bed rest, as well as operative delivery. Any of these conditions may precede maternal mortality. However, because multiple pregnancies are generally not registered as the cause of death, accurate mortality figures are unknown (3). Significant increases are seen in the frequency of maternal complications in iatrogenic compared to spontaneously conceived multiples. Nyirati et al (7) analyzed the outcomes of 232 spontaneous multiple compared to 98 induced twins and 16 induced triplets. Pregnancy induced hypertension was higher among induced twins compared to spontaneous twins and the incidence of pre-eclampsia was higher among induced triplets compared to spontaneous triplets.

Is There Evidence That Mothers >40 Who Have Iatrogenic Multiplies Constitute A New Obstetric Entity?

Infertile couples undergoing ART often tend to be older and are desperate to achieve a clinical pregnancy. Older maternal age, which is associated with a poor ovarian response and limited oocyte reserve become a challenge for the ART specialist. Luke (8) observed that the birth rate has been relatively stable during the past 20 years for women in their twenties and it's rising for women in their thirties and forties. The proportion of multiple births is much higher among older mothers and this percentage has risen dramatically since 1975. In 1998, the number of multiple births to mothers 45-year old was ten time higher than that among women in their thirties. The above-mentioned trends are directly related to assisted reproductive technologies, as well as the choices made by treating physicians.

References

(1) KEITH L, OLESZCZUK JJ, Iatrogenic multiple birth, multiple pregnancy and assisted reproductive technologies, Int J Gynecol Obstet, 64:11-25, 1999.

(2) NEWMAN RB, Obstetrical complications unique to multiple gestations, in Newman RB, Luke B (eds), Multifetal Pregnancies, Philadelphia PA, Lippincott Williams & Wilkins Softbound, 2000, pp 149-72.

(3) BLICKSTEIN I, KEITH L, The epidemic of multiple pregnancies, Postgraduate Obstet Gynecol, 21:1-6, 2001.

(4) PAPIERNIK E, DE MOUZON J, Perinatal results from triplet pregnancies and births from the register of French IVF centers: 1986-98, in Keith L, Blickstein I (eds), Triplet Pregnancies and Their Consequences, London, Parthenon Publishing Group, 2003.
(5) ALEXANDER G, KOGAN M, MARTIN J, What are the fetal growth patterns of singletons, twins and triplets in the USA, Clin Obstet Gynecol. 41:115-25, 1998.
(6) LUKE B, KEITH LG, The contribution of singletons, twins and triplets to low birth weight, infant mortality and handicap in the United States, J Reprod Med, 37:661-66, 1992.
(7) NYIRATI I, OUROS H, BARTFAI G, ET AL, Iatrogenic multiple pregnancy: Higher risk than a spontaneous one? J Reprod Med, 42:695-98, 1997.
(8) LUKE B, Perinatal significance of multiple gestation, in Newman R, Luke B (eds), Multifetal Pregnancy, Philadelphia PA, Lippincott Williams & Wilkins Softbound, 2000, pp 1-14.

Elective single embryo transfer with cryopreservation improves the outcome and diminishes the costs of IVF/ICSI

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BACKGROUND: Although elective single embryo transfer (eSET) minimizes the multiple birth rate after *in vitro* fertilization (IVF)/intra cytoplasmic sperm injection (ICSI), there remain concerns in many countries that it is less effective and more expensive than conventional double embryo transfer (DET).

METHODS: We compared the clinical outcome achieved in the years 1995–1999, in which eSET was rarely used (4.2% of women, DET period) with that of the years 2000–2004, in which eSET was more widely used (46.2%, eSET period). In the DET period, 826 women had 1359 fresh embryo cycles followed by 589 frozen–thawed embryo transfer (FET) cycles. In the eSET period, 684 women had 1027 fresh and 683 FET cycles. The cumulative term live birth rate/woman was the primary clinical outcome measure. An incremental cost-effectiveness ratio of a term live birth was also calculated based on hospital charges and medication prices of IVF/ICSI treatment.

RESULTS: The cumulative pregnancy rate/oocytes pickup (38.2 versus 33.1%, $P = 0.01$), cumulative live birth rate/oocytes pickup (28.0 versus 22.5%, $P = 0.002$) and cumulative live birth rate/woman (41.7 versus 36.6%, $P = 0.04$) were all higher in the eSET period than in the DET period. The cumulative multiple birth rate was significantly lower in the eSET period than in the DET period (8.9 versus 19.6%, $P < 0.0001$). A term live birth in the eSET period was 19 889 euros less expensive than in the DET period.

CONCLUSIONS: This study shows that eSET with cryopreservation is more effective and less expensive than DET and should be adopted as a treatment of choice.

Key words: in vitro fertilization/multiple pregnancy/elective single embryo transfer/cost-effectiveness

Submitted on September 11, 2008; resubmitted on January 20, 2009; accepted on January 27, 2009.

HFEA Statement on elective Single Embryo Transfer (eSET) guidelines

03 September 2008

The British Fertility Society (BFS) and the Association of Clinical Embryologists (ACE) have issued new guidelines in the journal Human Fertility to help UK clinics introduce an elective single embryo transfer (eSET) policy for IVF treatment.

Alan Doran, HFEA Interim Chief Executive, said:

"We are delighted to see the UK's fertility professionals take the next step in their campaign to tackle the single biggest risk of fertility treatment – the problem of multiple pregnancy and birth.

"These guidelines follow the professional's recognition of the 'overwhelming' case for action in this area and spell out to patients and clinic staff the appropriate treatment for particular groups of patients.

"This should be of great reassurance to patients by showing that nobody is suggesting a 'one size fits all' approach for fertility treatment."

Notes to editors

- The BFS and ACE are the main professional groups leading the One at a Time campaign, the national strategy to reduce the number of multiple pregnancies – the single biggest health risk of fertility treatment. See http://www.fertility.org.uk/ for further details.
- The national strategy is supported by: Association of Clinical Embryologists, British Fertility Society, British Infertility Counselling Association, Human Fertilisation and Embryology Authority, Infertility Network UK, Multiple Births Foundation, Royal College of Nursing, Royal College of Obstetricians and Gynaecologists, and the Royal College of Paediatrics and Child Health.
- The HFEA is the independent regulator for IVF treatment and embryo research. Our role is to protect patients and the public interest, to drive improvement in the treatment and research sectors and to provide information to the public and policymakers about treatment and research.
- The HFEA was set up in August 1991 as part of the Human Fertilisation and Embryology Act 1990. The HFEA's principal tasks are to license and monitor clinics that carry out in vitro fertilisation (IVF), artificial insemination (AI) and human embryo research. The HFEA also regulates the storage of gametes (eggs and sperm) and embryos.
- The HFEA publishes a **free Guide to Infertility** for people considering or starting fertility treatment.

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Page last updated: 11 March 2009

In Vitro Fertilization

IVF pregnancy outcomes

As with all normally conceived pregnancies, complications may occur following IVF treatment. The table below summarizes the overall outcome of IVF pregnancies compared to natural conception.

	IVF pregnancy	Natural conception	Comments
Miscarriage	14-30%	15-20%	Slight increase, due to older age.
Ectopic pregnancy	1-11%	0.2-1.4%	Increase due to many factors.
Preterm delivery	24-30%	6-7%	Four-fold increase.
Small birth weight	27-32%	5-7%	Five-fold increase.
Stillbirth rate	1.2%	0.6%	Two-fold increase.
Perinatal death	2.7%	1.0%	Two-fold increase.
Congenital abnormalities	0.8-5.4%	0.8-4.5%	No significant increase.
Caesarean section	33-58%	10-25%	Increase mainly because of multiple pregnancy and woman's age.
Multiple pregnancy			
twins	24-31%	1.2-4.5%	Increase due to higher number of embryos transferred.
triplets	0.5-5.2%	0.012%	
quadruplets	0.5%	0.0001%	

Outcome of children born following IVF treatment

Follow-up of children born as a result of IVF, ICSI and other forms of assisted conception is needed to study issues such as genetic risk, congenital malformation, psychological development, educational development, fertility, and risk of cancer. Current data demonstrated no significant differences in the incidence of congenital and chromosomal abnormalities in children conceived after IVF compared to children conceived naturally. Furthermore, children appear to develop normally both from fresh and frozen embryo transfer.

References

Aids to Obstetrics and Gynaecology, Fourth edition (ed.) G. M. Stirrat. 1997

Beral V, Doyle P. MRC Working Party on Children Conceived by In Vitro Fertilization: births in Great Britain resulting from assisted conception. 1978-1987. BMJ 1990; 300

Bergh T, Ericson A, Hillensjo T, Nygren K-G, Wennerholm U-B. Delivery and children born after in-vitro fertilization in Sweden 1982-95. The Lancet 1999. 354

HFEA Report 2005. Human Fertilisation and Embryology Authority. United Kingdom

Rizk B. The outcome of assisted reproductive technology. In A textbook of In Vitro Fertilization and Assisted Reproduction, Second edition (ed.) P. R. Brinsden. 1999

SART Report 2000. Fertility & Sterility.

One embryo as good as two for IVF success

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04 November 2009

[BioNews, London]

Transferring only one embryo during IVF (in vitro fertilisation) treatment significantly reduces the risk of multiple births without considerably altering a woman's chances of conceiving and having a baby, report Swedish researchers.

In a study published in the New England Journal of Medicine, comparing single with double embryo transfer, 53 per cent of the women who had a single embryo implanted had a live baby, compared with 57 per cent of women who were implanted with two embryos.

The study involved 660 women, 330 of whom were implanted with a single fresh embryo. If that treatment cycle failed, a second embryo was implanted which had been frozen then thawed before use. The remaining 330 women were implanted with two fresh embryos.

Dr William Gibbons, the president of the American Society for Reproductive Medicine, said that these findings 'should provide comfort for those who want to perform single-embryo transfers that the pregnancy rates are equivalent'.

The study also showed that the rate of multiple births among women first implanted with a single fresh embryo was significantly lower, at just 2.3 per cent. Of the women implanted with two fresh embryos, 27.5 per cent gave birth to more than one baby.

IVF treatment has routinely involved the implantation of multiple embryos in order to increase a woman's chances of having a child, but as IVF procedures have become more advanced, doctors have been able to implant fewer embryos, with equally successful results. However, multiple births are a common result, and incur health risks for both the mother and baby. Gestational diabetes, bleeding and pre-eclampsia, are all a risk for the mother, and the baby is at increased risk of cerebral palsy, birth defects and developmental delays.

The costs of IVF often prohibit more people choosing single embryo transfer, particularly in countries such as the US where treatment is not covered by national healthcare providers or insurance.

Moreover, 'the stress and disappointment of a failed cycle is hard to put a value on' says Dr Laurel Stadtmauer, an associate professor of obstetrics and gynecology at the Jones Institute for Reproductive Medicine in Norfolk, Virginia, US. 'This research adds further evidence confirming the value of elective single embryo transfer in assisted reproductive technologies,' said Richard Kennedy, a spokesman for the International Federation of Fertility Services.
