Human Reproduction vol.15 no.6 pp.1217–1219, 2000

DEBATE

Avoiding multiple pregnancies in ART

Consideration of new strategies

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This debate was previously published on Webtrack, March 1, 2000

To maximize pregnancy rates, physicians who perform IVF, often transfer multiple embryos, which increases the multiple birth risk. Multiple birth infants are at significant risk for a number of adverse outcomes including preterm delivery, low birth weight, congenital malformations, fetal and infant deaths and long term morbidity and disability among survivors. Since the ultimate goal for an IVF treatment is the birth of a healthy infant, an important issue for all kinds of assisted reproductive technologies (ART) must be the reduction or elimination of multiple pregnancies. In this article, different strategies to avoid multiple births in ART are discussed.

Key words: assisted reproductive technologies/IVF/multiple pregnancies

Introduction

The incidence of multiple pregnancy and delivery has increased dramatically over the past decades in many developed countries. The Swedish registry study of all IVF births in Sweden 1982–1995 showed that the incidence of twin deliveries in Sweden increased by 79% between 1973 and 1995 (Bergh *et al*., 1999a). About one third of the increase in the frequency of twin births was because of the increasing age of the mothers in the general population since natural twin pregnancies are known to occur with greater frequency among older mothers (Waterhouse 1950, Spellacy *et al.*, 1990, Jewell and Yip, 1995), one third was because of IVF and the remaining third probably because of ovarian stimulation.

In IVF, the usual practice of transferring two or more embryos to achieve higher pregnancy rates results in a high incidence of multiple births. In the World Collaborative Report on IVF figures for 1995 showed that 24.7% of the pregnancies were twin, 4.1% were triplet and 0.2% were quadruplet (De Mouzon and Lancaster, 1997). Consequently, 44–45% of the newborns were born as multiple birth babies.

Multiple pregnancy carries additional risks for both mother and offspring and more elaborate monitoring of the pregnancy is required. Obstetric complications associated with multiple pregnancy include prenatal screening problems, an increased incidence of pre-eclampsia and eclampsia, antepartum haemorrhage, preterm labour, intrauterine growth retardation and surgical and assisted delivery. Among neonatal complications the most common are low birth weight, due to prematurity and/or placental dysfunction and congenital malformations. The perinatal mortality is 5–6 times higher among twins compared with singletons.

The Swedish registry study showed a 20-fold increased risk of being born as a multiple birth baby for an IVF child compared with the general population (Bergh *et al*, 1999a). The pregnancy and neonatal complications observed in IVF pregnancies were almost entirely due to multiple pregnancies, the majority of which were twin pregnancies. The rate of prematurity (<37 weeks) among twin pregnancies was 47.3% compared with 11.2% among singletons. The corresponding figures for low birth weight were 43.8 and 8.9% respectively.

In the Swedish study, children born after IVF had an increased risk of malformations, relative risk 1.39 (95% confidence intervals, 1.25–1.54) compared with the general population. This increase could at least partly be explained by the much higher proportion of multiple birth babies in the IVF group. An increased incidence of anencephaly, hydrocephalus and atresia of the oesophagus was found. Ten infants (0.2%) in the IVF had neural tube defects (anencephaly or spina bifida) compared with the expected number of three to four. Seven of the 10 infants with neural tube defects and six out of seven children with hydrocephalus were from sets of twins.

Multiple pregnancies are also associated with increased infant and childhood morbidity such as cerebral palsy and mental retardation. Two recent studies of the incidence of cerebral palsy reported dramatically increased risks in multiple births: twins had risks approximately five times higher and triplets 17 times higher than in singletons (Peterson *et al*., 1993) and the risk of producing at least one child with cerebral palsy was estimated to 1–5% for twin, 8% for triplet and almost 50% for quadruplet pregnancies (Yokohama *et al.,* 1995). Lower gestational age, lower birth weight distribution and being a twin all independently increased the risk of cerebral palsy in twin pregnancies (Pharoah and Cooke, 1996; Williams *et al*., 1996).

Most studies of child development after IVF carried out to

date include relatively small numbers of children and have a limited period of follow-up and consequently the risks for long term handicap, e.g. cerebral palsy and mental retardation for children born after IVF compared with the general population have so far not been possible to evaluate. In an ongoing Swedish follow-up study of the national IVF birth cohort (n = 5856 children) from 1982–1995, childhood morbidity, i.e. cerebral palsy, mental retardation, severe neurological and visual impairment, will be analysed and compared with data in a control group from the general population.

Which methods are available today to reduce the number of multiple births after ART?

An overall change in transfer policy to transfer only one embryo at a time would certainly result in mainly singletons. Such a strategy has never been tested on a large scale but would probably result in a decrease in pregnancy and birth rates. This may be unacceptable both to patients and practitioners, who all aim at the best possible rates of success, measured today as pregnancy per cycle. An alternative to an overall one-embryo transfer would be an individualized embryo transfer policy. Theoretical models for one-embryo transfers in selected groups of patients at high risk of multiple births have recently been discussed (Coetsier and Dhont, 1998; Strandell *et al*., 1999; Van Royen *et al*., 1999). It seems possible to identify a subgroup of patients with an increased risk of multiple birth and offer them one-embryo transfers. A possible slight decrease in birthrate per transfer for these women may well be compensated by additional transfers of frozen–thawed embryos. The overall probability of a delivery per initiated cycle would thereby be minimally jeopardized. In a recent publication (Vilska *et al*., 1999) elective one-embryo transfer showed a satisfactory pregnancy rate (29.7%/transfer) in a selected group of patients, the pregnancy rate being similar to the ordinary routine two embryo transfer programme. A Belgian group has recently reported results from a small, prospective, randomized trial in women aged <34 years and with at least two top quality embryos (Gerris *et al*., 1999). A total of 53 women were randomized to one or two embryo transfers and satisfactory results were achieved in both groups.

Embryo/fetal reduction, as a third strategy to reduce the number of multiple births have been used worldwide. Despite that collaborative data (Evans *et al.*, 1996) have reported satisfactory outcome for the children and limited risks for the mother this kind of intervention raises serious ethical and psychological problems (Schreiner-Engel *et al.*, 1995; Bergh *et al.*, 1999b). It may be indicated in cases of particularly high order multiple pregnancies but can never be justified as a method for reduction of twins.

A fourth strategy to reduce multiple births is the adoption by ART clinics of a new measure for success, 'birth per embryo transferred'. The most common statistics used by ART units to indicate success and excellence both with regard to research or for the sake of prestige, unfortunately all promote the replacement of a high number of embryos. Pregnancy rate per treatment cycle, per aspiration or per replacement cycle,

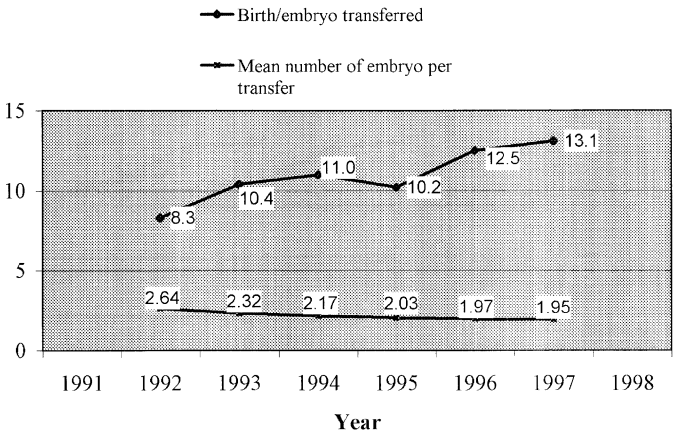

Figure 1. Birth rate per embryo transferred (%) and the mean number of embryos transferred. National data from all IVF and intracytoplasmic sperm injection (ICSI) cycles in Sweden 1992–1997 (by permission of P.O.Karlström).

are all increased by increasing the number of embryos replaced. The same applies for 'baby take home rate' and 'number of babies born'. Unfortunately, the result is obtained at the expense of the increased fetal morbidity associated with high order multiple pregnancy.

'Birth per embryo transferred' is a statistical criterion that promotes a policy aiming at singleton pregnancies; it is negatively affected by the incidence of multiple pregnancies since results are best when a low number of embryos are transferred. A disadvantage of this statistic is that its significance is not yet understood by patients, patient organizations, politicians and clinicians. Clinics like to use statistics that indicate high success rates, such as pregnancy rate or number of babies born. 'Birth per embryo transferred' appears at first sight to lower success rates, but actually reflects the chance of getting a healthy baby. High figures mean a high incidence of singleton pregnancies. To the couple with infertility problems results may easily be explained as the probability that they will become parents. ART results in Sweden, described in this manner, are shown in Figure 1. In ART units results are affected by the allocation of individual patients to optimal treatment, aiming at a singleton pregnancy. This is the reason for the declining number of embryos transferred. One explanation for the increasing births/embryo transferred may be a better selection of high quality embryos.

Conclusions

Thus, in order to decrease the incidence of obstetric problems and fetal morbidity/mortality in multiple pregnancy after ART, we suggest that: (i) clinics endeavour to implement one-embryo transfers; (ii) two-embryo transfer be used only for those women that are at low risk of multiple pregnancy; and (iii) ART results should be presented as 'Birth per embryo transferred' and this term should be given the status of 'the criterion of ART excellence'

Acknowledgement

This work was supported by Organon.

References

Bergh, T., Ericson, A., Hillensjö, T. *et al.* (1999a) Deliveries and children born after IVF treatment in Sweden 1982–1995 – a retrospective cohort study. *Lancet*, **354**, 1579–1585.

Bergh, C., Möller, A., Nilsson, L. and Wikland, M. (1999b) Obstetric outcome and follow up of pregnancies following embryo reduction. *Hum. Reprod.*, **13**, 2170–2175.

Coetsier, T. and Dhont, M. (1998) Avoiding multiple pregnancies in in-vitro fertilization: who's afraid of single embryo transfer? *Hum. Reprod.*, **13**, 2663–2664.

De Mouzon, J. and Lancaster, P. (1997) World Collaborative Report on *in vitro* fertilization, preliminary data for 1995. *J. Assist. Reprod. Genet.*, **14S**, 251–265.

Evans, M.I., Dommergues, M., Wapner, R.J. *et al.* (1996) International collaborative experience of 1978 patients having multifetal pregnancy reduction: a plateauing of risks and outcomes. *J. Soc. Gynecol. Invest.*, **3**, 23–26.

Gerris, J., De Neubourg, D., Mangelschots, K. *et al.* (1999) Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial. *Hum Reprod*, **14**, 2581–2587.

Jewell, S. and Yip, R. (1995) Increasing trends in plural births in the United States. *Obstet. Gynecol.*, **85**, 229–232.

Petterson, B., Nelson, K., Watson, L. and Stanley, F. (1993) Twins, triplets and cerebral palsy in births in Western Australia in the 1980s. *Br. Med. J.*, **307**, 1239–1243.

Pharoah, P. and Cooke, T. (1996) Cerebral palsy and multiple births. *Arch. Dis. Child.*, **75**, F174–F177.

Schreiner-Engel, P., Walther, V., Mindes, J. *et al.* (1995) First trimester multifetal pregnancy reduction: acute and persistent psychological reactions. *Am. J. Obstet. Gynecol.*, **172**, 541–547.

Spellacy, W., Handler, A. and Ferre, C. (1990) A case control study of 1235 twin pregnancies from a 1982–1987 perinatal database. *Obstet. Gynecol.*, **75**, 168–171.

Strandell, A., Bergh, C., Lundin, K. and Hamberger, L. (1999) Factors for predicting multiple pregnancies in fresh IVF cycles can be used for selection of patients suitable for one-embryo transfer. *Hum. Reprod.*, **14**, 166–167

Van Royen, E., Mangelschots, De Neubourg, D. *et al.* (1999) Characterization of top quality embryo, a step towards single-embryo transfer. *Hum Reprod*, **14**, 2345–2349.

Vilska, S., Tiitinen, A., Hyden-Granskog, C. and Hovatta, O. (1999) Elective transfer of one embryo results in an acceptable pregnancy rate and eliminates the risks of multiple birth. *Hum. Reprod.*, **14**, 2392–2395.

Waterhouse, J. (1950) Twinning in twin pedigrees *Br. J. Soc. Med.*, **4**, 197.

Williams, K., Henessy, E. and Alberman, E. (1996) Cerebral palsy: effects of twinning, birthweight, and gestational age. *Arch. Dis. Child.*, **75**, F178–F182.

Yokohama, Y., Shimizu, T. and Hayakawa, K. (1995) Prevalence of cerebral palsy in twins, triplets and quadruplets. *Int. J. Epidemiol.*, **24**, 943–948.