

DEBATE

Safety issues in assisted reproduction technology

The children of assisted reproduction confront the responsible conduct of assisted reproductive technologies

Raymond D.Lambert

Centre de Recherche en Biologie de la Reproduction (CRBR), Department of Obstetrics and Gynecology, Laval University and Ontogeny and Reproduction Research Unit, CHUL Research Center (CHUQ), Canada

Corresponding address: CRBR, T1 49, CHUL/CHUQ, 2705 Boul. Laurier, Québec, Canada, QC G1V 4G2.

E-mail: ray.lambert@crchul.ulaval.ca

Neurological sequelae and multiple birth defects have been observed in children conceived by IVF and ICSI. Multiple pregnancy is the most important risk factor. These health problems challenge the responsible practice of medicine. The core values of medicine and the deontology of the profession have been reviewed to define the responsible conduct of research and clinical practice. Professional associations have proposed guidelines to reduce health problems in assisted reproductive technology. Although these health problems could have been prevented, this response by the medical community is nonetheless an important step towards improving responsible medical practices that have become questionable over the years. Professional associations must find out means, not only to implement their guidelines, but also to prevent the recurrence of such episodes in the history of medicine.

Key words: assisted reproductive technologies/clinical responsibility/ethics/health problems/multiple pregnancies

Introduction

Assisted reproductive technology (ART) has enabled many couples to achieve long-awaited dreams of having children. But, recently, it was demonstrated that children conceived through IVF experienced more complications than the general population (Strömberg *et al.*, 2002). Although singleton infants born after IVF had a greater risk of low birth weight (Schieve *et al.*, 2002) or multiple birth defects (Hansen *et al.*, 2002; Koivurova *et al.*, 2002) than naturally conceived infants, twin pregnancy is clearly the most important risk factor (Hansen *et al.*, 2002; Koivurova *et al.*, 2002; Schieve *et al.*, 2002; Strömberg *et al.*, 2002). Multiple pregnancies result in a higher frequency of perinatal mortality (Luke and Keith, 1992; Gissler *et al.*, 1995; Tarin and Cano, 1995; Lieberman, 1998; Murdoch, 1998), morbidity (Luke and Keith, 1992; Seamark and Robinson, 1995; Murdoch, 1998; Keith *et al.*, 2000) and psychological sequelae (Olivennes *et al.*, 2001; White and Leuthner, 2001). Furthermore, obstetrical and perinatal costs are considerably higher for twins and triplets than for singletons (Callahan *et al.*, 1994; Souter and Murphy Goodwin, 1998; ESHRE Capri Workshop Group, 2000; White and Leuthner, 2001).

These health problems and costs are a tragedy for the infant and the family and cause concern among health-care providers and policymakers [Centers for Disease Control and Prevention (US), 2000]. Therefore, it challenges the responsible practice

of medicine and the regulation in the field of reproductive medicine.

The aim of this paper is to explore the responsible practice of assisted reproductive technology in the light of the core values of medicine and the deontology of the profession.

Core values of medicine

Traditionally, the goals of medicine have been to: (i) preserve and extend life, (ii) promote and maintain health, and (iii) relieve pain and suffering. The Declaration of Helsinki (World Medical Association; Article 2) is explicitly clear in this effect: 'It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty'.

An international group of experts, re-examining these goals in light of 'contemporary possibilities and problems', suggested four goals 'representing the core values of medicine' (Callahan, 1996): the prevention of disease and injury and promotion and maintenance of health; the relief of pain and suffering caused by disease; the care and cure of those with a disease, and the care of those who cannot be cured; and, the avoidance of premature death and the pursuit of a peaceful death'.

Medical practices should always be based on these values and responsibilities as they are primordial in respecting human dignity as expressed by the search of morally acceptable ends and morally acceptable means to those ends.

Professional medical guidelines: rethinking medical practices in assisted reproductive technology

Taking medical values into consideration, several medical associations that have recognized the health problems and obstetrical and perinatal costs that arise from infertility treatments have defined guidelines to prevent or to reduce these undesirable pregnancies. Three types of medical solutions have been introduced, namely a tighter control of the uses of ovarian drugs, the transfer of fewer IVF embryos, and the non-selective embryo reduction (Aberg *et al.*, 1978; Maymon *et al.*, 1995). The two last options will be discussed here.

Reducing the number of embryos transferred

The European Society of Human Reproduction and Embryology (ESHRE) has recently reviewed its guidelines on good practices in IVF laboratories (ESHRE Campus Course Report, 2001). Because the goal of infertility treatment is to aid prospective parents—as much as possible and with the least harm—in achieving their desire to have children, the general view of ESHRE is that gynaecologists should always aim for singleton pregnancies. Methods of single embryo transfer (SET) have been refined to result in acceptable pregnancy and multiple pregnancy rates (Gerris *et al.*, 1999; Van Royen *et al.*, 1999; Vilska *et al.*, 1999; ESHRE Campus Course Report, 2001; Tiitinen *et al.*, 2001). Maintaining these rates is made feasible by improved techniques to help predict an embryo's chances of survival (Steer *et al.*, 1992; Visser and Fourie, 1993) and the pattern of cell division, the absence of a multinucleated blastomere and a low degree of fragmentation correlate with the quality of the embryo and the implantation rate (Gerris *et al.*, 1999; Van Royen *et al.*, 1999; Vilska *et al.*, 1999; Milki *et al.*, 2000; The ESHRE Capri Workshop Group, 2000; Tiitinen *et al.*, 2001; Van Royen *et al.*, 2001). In this respect, culturing the conceptus for 3 days and transferring a single embryo (elective SET) might be the right option since no advantage of blastocyst transfer over day 3 transfer has been shown (Rienzi *et al.*, 2002; Utsunomiya *et al.*, 2002). Considering the above information, elective SET, particularly in selected groups of patients at high risk of multiple pregnancies, is the sole solution to the epidemic problem of post-IVF/ICSI twin pregnancies, probably at whatever stage the transfer is conducted. This group is characterized as being young, undergoing their first or second IVF cycle, or as having had prior births (Gerris *et al.*, 1999; Vilska *et al.*, 1999; Hazekamp *et al.*, 2000; Engmann *et al.*, 2001; ESHRE Campus Course Report, 2001; Ozturk *et al.*, 2001; Strandell *et al.*, 2002).

As indicated in the ESHRE Campus Report on prevention of twin pregnancies after IVF/ICSI (ESHRE Campus Course Report, 2001), 'Common sense dictates that elective SET as a concept should be applied from now onward... Elective SET should be recommended without further delay if at least two conditions are fulfilled: the patient is twin prone; this definition needs to be further fine-tuned in well-designed clinical studies, but currently includes: age (definitely if <34; probably if <38 years of age) and rank of trial (first trial, probably second trial as well); if a 'top-quality embryo' can be transferred'.

The American Society for Reproductive Medicine (ASRM)

has adopted a much more tolerant approach (American Society for Reproductive Medicine, 1999): 'In patients with the most favorable prognosis usually no more than two good quality embryos should be transferred...' (Article II.A). In low prognosis patients: '...no more than five good quality embryos should be transferred' (Article II.D).

The couple should be thoroughly informed of the risks of multiple gestation in cases where more than one embryo is transferred (American Society for Reproductive Medicine, 1999; Gianaroli *et al.*, 2000). Indeed, the transfer of two good quality embryos in the good prognosis patients leads to unacceptable frequency of twin gestations (around 40%) (Staessen *et al.*, 1995; Milki *et al.*, 1999), thus increasing health problems for both the newborn infant and the mother (Bergh *et al.*, 1999). Once informed of these obstetrical and neonatal risks, couples can be easily persuaded to opt for transfer of two embryos, and patients with good prognoses can be advised to accept the transfer of a single embryo (Coetsier and Dhont, 1998).

Non-selective fetal reduction

The rationale behind fetal reduction is that by reducing the number of fetuses one decreases the incidence of biological complications. Only a limited number of studies have compared the outcome of multiple gestations with and without embryo/fetal reduction; however, according to the literature, an improvement in outcomes for the infant and the mother has been reported (Souter and Murphy Goodwin, 1998).

Fetal reduction decreases the incidence of spontaneous abortion, preterm birth, low birth weight, and very low birth weight infants (Lipitz *et al.*, 1994; Berkowitz *et al.*, 1996; Evans *et al.*, 1996; Kadhel *et al.*, 1998; Souter and Murphy Goodwin, 1998). This effect seems more significant in quadruple and higher order multiple gestations (Berkowitz *et al.*, 1996). Certain studies have reported no reduction in fetal mortality in triplet pregnancy (Porreco *et al.*, 1991; Lipitz *et al.*, 1996; Angel *et al.*, 1999), but numerous other reports (Macones *et al.*, 1993; Lipitz *et al.*, 1994; Smith-Levitin *et al.*, 1996; Yaron *et al.*, 1999; Boulot *et al.*, 2000), and a review (Fasouliotis and Schenker, 1997) suggest a reduction in severe prematurity, low birth weight, spontaneous abortion and perinatal mortality, a potential reduction in severe psychological and social problems and hospitalization in neonatal intensive care units (Kadhel *et al.*, 1998). Additionally, Caesarean deliveries are less frequent once triplets are reduced to twins, compared with non-reduced triplet pregnancies (Kadhel *et al.*, 1998).

However, inherent medical risks to the remaining embryo are part of the possible consequences of fetal reduction, as ~8% of procedures lead to spontaneous abortion of all the fetuses for triplet or quadruplet pregnancies, and this value rises to 17.6% when it is applied to sextuplets or more (Souter and Murphy Goodwin, 1998; Coffler *et al.*, 1999).

Taking into account the biological, psychological, and ethical issues of fetal reduction, the American College of Obstetricians and Gynecologists, the ASRM, and the ESHRE Capri Workshop Group recommend primary prevention as the first solution to multiple pregnancies (ACOG, 1999; American Society for

Reproductive Medicine, 1999; ESHRE Capri Workshop Group, 2000). Indeed, finding technically and medically feasible means to prevent multiple gestations would obviate the need for nonselective fetal reduction.

Discussion

The responsible conduct of medicine in reproductive biology

The above analysis shows that the medical community can find satisfactory solutions to iatrogenic problems. Confronted with health risks caused by the treatment of infertility, a list of corrective measures that considerably reduce these problems has been proposed. Some current guidelines are aimed not only at the treatment of infertility, but also encompass a broad range of outcomes of ART pregnancies. Working with such methods has shown to be beneficial to the health of both mother and child. Experts even suggest that producing healthy singleton births should indeed be the main objective of an IVF centre (ESHRE Campus Course Report, 2001): 'The long-term welfare of the family should take precedence over the short term goal of achieving a pregnancy and ambiguous preoccupation with success figures. Indeed, a healthy child is the ultimate goal of IVF-treatment... the professional competence of an IVF center should be measured in terms of ongoing singleton pregnancies per cycle' (p. 798).

Risks must always be weighed against the advantages, and when alternative solutions presenting minimal risks are available, the risky procedures should be eliminated. It is unethical to do harm when safer techniques are available. In the context of infertility treatment, it is unethical to apply clinical procedures likely to result in higher multiple pregnancy rates when it is possible to produce a singleton pregnancy. The attitude of ESHRE clearly suggests that medical associations can respond responsibly to the challenge raised by the consequence of infertility treatment. It also indicates that self-regulation might be possible in the field, but that it will not happen until professional associations have found ways and means to implement their ethical and medical guidelines.

Retrospective analysis of health problems in assisted reproductive technology

The detrimental health consequences of pregnancies resulting from the transfer of several IVF embryos raise a fundamental question: at the time of introducing ART into medical practice, and therefore at the time when the procedure was still experimental, would it have been possible to predict and prevent the negative outcomes of IVF pregnancies? Research on laboratory and domestic animals and the practices of embryo transfer in veterinary medicine has shown that multiple embryo transfer resulted in multiple gestation. This correlation was demonstrated a long time ago and was well known by the time of the birth of the first test-tube baby. At that time the medical risks of multiple gestations had already been documented (Itzkowic, 1979; Ron-El *et al.*, 1981). Soon after the introduction of ART, multiple gestations resulting from the transfer of IVF embryos were acknowledged. Everyone in the field had access to these data, and restricting the number of embryos transferred after IVF was swiftly proposed (Kerin *et al.*, 1983).

Looking retrospectively at these data, it seems perplexing that during the 1980s the transfer of multiple IVF embryos was commonly accepted in medical practice. How could this have happened in light of the Nuremberg Code precluding any human experimentation '... where there is *a priori* reason to believe that death or disabling injury will occur...' (Nuremberg Code)? Protecting human subjects has for a long time been a condition imposed on medical experimentation and treatment. Such protection is at the heart of the respect for human dignity (Council of Europe, 1997; The Medical Research Council *et al.*, 1998).

Respect for human dignity is a moral imperative that translates into a number of important correlative ethical principles directly related to the question in hand. Among these, physicians have the duty to ensure that patient consent is informed and not coerced. Patients must be thoroughly informed of the possible health problems arising from the use of ovulation-inducing agents or from the transfer of several IVF embryos. Physicians must avoid, prevent, or minimize any harm that could be done to their patients.

Experimental or novel treatments should be administered only if adequate safety has been documented; pre-clinical studies must first show a minimum degree of safety before the conduct of clinical trials continues in accordance with basic ethical principles. This follows the Declaration of Helsinki (World Medical Association), statements 10 and 11: 'It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subjects.' (Article 10). 'Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.' (Article 11). On the basis of these principles, the transfer of multiple IVF embryos should have not even reached phase I in the clinical trials, much less should it have become a widely accepted medical practice.

Issues for debate

Gynaecologists are treating efficiently, but not always safely, their patients. The birth of a healthy child, which should be the most important indicator of a successful infertility treatment, has been neglected. In this difficult context, how can we define the responsible practice of medicine and the responsible conduct of research?

Physicians and scientists must have and use the knowledge and experience needed to aid the treatment of infertility. Their actions must result in the births of healthy babies, as ESHRE is recommending. This requires proficiency. Such a goal cannot be reached without knowing the health risks of multiple pregnancies and without knowing and prescribing the appropriate treatment to prevent undesirable outcomes. This cannot be done responsibly without great knowledge of universal ethical principles and local and professional guidelines dealing with human experimentation or medical treatment, such as safety of the procedures, beneficence, justice, respect of autonomy: all included and at work in the respect of human dignity. Once ethical evaluation has been performed, practices may have to be changed as in the case of the transfer of several

IVF embryos. Physicians and biomedical researchers must be sufficiently proficient to find alternatives or to develop new ethically acceptable medical solutions to prevent iatrogenic problems. This last responsibility must be delegated to those who have the competency to resolve biomedical issues—this role belongs incontestably to physicians and bioscientists.

Conclusions

Professional associations have already begun to define guidelines aimed at the ultimate goal of respecting human dignity. Now comes the responsibility to find means, not only to implement these guidelines, but also to take all possible measures to prevent such regrettable episodes of medical history from ever happening again.

Acknowledgement

This work was supported by CIHR 'Strategic Training Program Grants (Grant New)' grant No 200112STP-98239-TGA-CFBA-10115.

References

- Aberg, A., Mitelman, F., Cantz, M. and Gehler, J. (1978) Cardiac puncture of a fetus with Hurler's disease avoiding abortion of unaffected co-twin. *Lancet*, **ii**, 990–991.
- ACOG (1999) Nonselective embryo reduction: ethical guidance for the obstetrician-gynecologist. *Int. J. Gynecol. Obstet.*, **65**, 216–219.
- American Society for Reproductive Medicine (1999) Guidelines on number of embryos transferred. <http://www.asrm.org/Media/Practice/practice.html>.
- Angel, J. L., Kalter, C. S., Morales, W. J., Rasmussen, C. and Caron, L. (1999) Aggressive perinatal care for high-order multiple gestations: Does good perinatal outcome justify aggressive assisted reproduction techniques? *Am. J. Obstet. Gynecol.*, **181**, 253–259.
- Bergh, T., Ericson, A., Hillensjö, T., Nygren, K.G. and Wennerholm, U.B. (1999) Deliveries and children born after *in-vitro* fertilisation in Sweden 1982–95: a retrospective cohort study. *Lancet*, **354**, 1579–1585.
- Berkowitz, R.L., Stone, J. and Alvarez, M. (1996) The current status of multifetal pregnancy reduction. *Am. J. Obstet. Gynecol.*, **174**, 1265–1272.
- Boulot, P., Vignat, J., Vergnes, C., Dechaud, H., Faure, J. M. and Hedon, B. (2000) Multifetal reduction of triplets to twins: a prospective comparison of pregnancy outcome. *Hum. Reprod.*, **15**, 1619–1623.
- Callahan, D. (1996) An international project of the Hastings Center. The goals of medicine. Settings new priorities. *Hastings Ctr Report*, **26**, (Suppl.) S2–4.
- Callahan, T.L., Hall, J.E., Ettner, S.L., Christiansen, C.L., Greene, M.F. and Crowley, W.F.J. (1994) The economic impact of multiple-gestation pregnancies and the contribution of assisted-reproduction techniques to their incidence. *N. Engl. J. Med.*, **331**, 244–249.
- Centers for Disease Control and Prevention (US) (2000) Contribution of assisted reproductive technology and ovulation-inducing drugs to triplet and higher-order multiple births. United States, 1980–1997. *JAMA*, **284**, 299–300.
- 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.
- Coffler, M. S., Kol, S., Drugan, A. and Itskovitz-Eldor, J. (1999) Early transvaginal embryo aspiration: a safer method for selective reduction in high order multiple gestations. *Hum. Reprod.*, **14**, 1875–1878.
- Council of Europe (1997) Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: convention on human rights and biomedicine (adopted by the Committee of Ministers on 19 November 1996). *Hum. Reprod.*, **12**, 2076–2080.
- Engmann, L., Maconochie, N., Tan, S. L. and Bekir, J. (2001) Trends in the incidence of births and multiple births and the factors that determine the probability of multiple birth after IVF treatment. *Hum. Reprod.*, **16**, 2598–2605.
- ESHRE Capri Workshop Group (2000) Multiple gestation pregnancy. *Hum. Reprod.*, **15**, 1856–1864.
- ESHRE Campus Course Report (2001) Prevention of twin pregnancies after IVF/ICSI by single embryo transfer. *Hum. Reprod.*, **16**, 790–800.
- Evans, M. I., Dommergues, M., Wapner, R. J., Goldberg, J. D., Lynch, L., Zador, I. E., Carpenter, R. J., Timor-Tritsch, I., Brambati, B. *et al.* (1996) International, collaborative experience of 1789 patients having multifetal pregnancy reduction: A plateauing of risks and outcomes. *J. Soc. Gynecol. Invest.*, **3**, 23–26.
- Fasoulitis, S. J. and Schenker, J. G. (1997) Multifetal pregnancy reduction: a review of the world results for the period 1993–1996. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **75**, 183–190.
- Gerris, J., De Neubourg, D., Mangelschots, K., Van Royen, E., Van de Meerssche, M. and Valkenburg, M. (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.
- Gianaroli, L., Plachot, M., va Kooij, R., Al-Hasani, S., Dawson, K., DeVos, A., Magli, M. C., Mandelbaum, J., Selva, J. and van Inzen, W. (2000) ESHRE guidelines for good practice in IVF laboratories. *Hum. Reprod.*, **15**, 2241–2246.
- Gissler, M., Silverio, M. M. and Hemminki, E. (1995) *In-vitro* fertilization pregnancies and perinatal health in Finland 1991–1993. *Hum. Reprod.*, **10**, 1856–1861.
- Hansen, M., Kurinczuk, J. J., Bower, C. and Webb, S. (2002) The risk of major birth defects after intracytoplasmic sperm injection and *in vitro* fertilization. *New. Engl. J. Med.*, **346**, 725–730.
- Hazekamp, J., Bergh, C., Wennerholm, U.-B., Hovatta, O., Karlstrom, P. O. and Selbing, A. (2000) Avoiding multiple pregnancies in ART. Consideration of new strategies. *Hum. Reprod.*, **15**, 1217–1219.
- Itzkowicz, D. (1979) A survey of 59 triplet pregnancies. *Br. J. Obstet. Gynaecol.*, **86**, 23–28.
- Kadhel, P., Olivennes, F., Fernandez, H., Vial, M. and Frydman, R. (1998) Are there still obstetric and perinatal benefits for selective embryo reduction of triplet pregnancies? *Hum. Reprod.*, **13**, 3555–3559.
- Keith, L. G., Oleszczuk, J. J. and Keith, D. M. (2000) Multiple gestation: reflections on epidemiology, causes, and consequences. *Int. J. Fertil. Womens Med.*, **45**, 206–214.
- Kerin, J.F., Warnes, G.M., Quinn, P.J., Jeffrey, R., Kirby, C., Matthews, C.D., Seamark, R.F. and Cox, L.W. (1983) Incidence of multiple pregnancy after *in vitro* fertilisation and embryo transfer. *Lancet*, **2**, 537–540.
- Koivurova, S., Hartikainen, A.-L., Gissler, M., Hemmenki, E., Sovio, U. and Jarvelin, M.-R. (2002) Neonatal outcome and congenital malformations in children born after *in-vitro* fertilization. *Hum. Reprod.*, **17**, 1391–1398.
- Lieberman, B. (1998) An embryo too many? *Hum. Reprod.*, **13**, 2664–2666.
- Lipitz, S., Reichman, B., Uval, J., Shalev, J., Achiron, R., Barkai, G., Lusky, A. and Mashlach, S. (1994) A prospective comparison of the outcome of triplet pregnancies managed expectantly or by multifetal reduction to twins. *Am. J. Obstet. Gynecol.*, **170**, 874–879.
- Lipitz, S., Uval, J., Achiron, R., Schiff, E., Lusky, A. and Reichman, B. (1996) Outcome of twin pregnancies reduced from triplets compared with nonreduced twin gestations. *Obstet. Gynecol.*, **87**, 511–514.
- Luke, B. and Keith, L.G. (1992) The contribution of singletons, twins and triplets to low birth weight, infant mortality and handicap in the United States. *J. Reprod. Med.*, **37**, 661–666.
- Macones, G. A., Schemmer, G., Pritts, E., Weinblatt, V. and Wapner, R. J. (1993) Multifetal reduction of triplets to twins improves perinatal outcome. *Am. J. Obstet. Gynecol.*, **169**, 982–986.
- Maymon, R., Herman, A., Shulman, A., Halperin, R., Arieli, S., Bukovsky, I. and Weinraub, Z. (1995) First trimester embryo reduction: a medical solution to an iatrogenic problem. *Hum. Reprod.*, **10**, 668–673.
- Milki, A.A., Fisch, J.D. and Behr, B. (1999) Two-blastocyst transfer has similar pregnancy rates and a decreased multiple gestation rate compared with three-blastocyst transfer. *Fertil. Steril.*, **72**, 225–228.
- Milki, A.A., Hinckley, M.D., Fisch, J.D., Dasig, D. and Behr, B. (2000) Comparison of blastocyst transfer with day 3 embryo transfer in similar patient populations. *Fertil. Steril.*, **73**, 126–129.
- Murdoch, A.P. (1998) How many embryos should be transferred? *Hum. Reprod.*, **13**, 2666–2669.
- Nuremberg Code Article 5. <http://ohsr.od.nih.gov/nuremberg.php3>.
- Olivennes, F., Mannaerts, B., Struijs, M., Bonduelle, M. and Devroey, P. (2001) Perinatal outcome of pregnancy after GnRH antagonist (ganirelix) treatment during ovarian stimulation for conventional IVF or ICSI: a preliminary report. *Hum. Reprod.*, **16**, 1588–1591.
- Ozturk, O., Bhattacharya, S. and Templeton, A. (2001) Avoiding multiple pregnancies in ART. Evaluation and implementation of new strategies. *Hum. Reprod.*, **16**, 1319–1321.

- Porreco, R. P., Burke, M. S. and Hendrix, M. L. (1991) Multifetal reduction of triplets and pregnancy outcome. *Obstet. Gynecol.*, **78**, 335–339.
- Rienzi, L., Ubaldi, F., Iacobelli, M., Ferrero, S., Minasi, M.G., Martinez, F., Tesarik, J. and Greco, E. (2002) Day 3 embryo transfer with combined evaluation at the pronuclear and cleavage stages compares favourably with day 5 blastocyst transfer. *Hum. Reprod.*, **17**, 1852–1855.
- Ron-El, R., Caspi, E., Schreyer, P., Weinraub, Z., Arieli, S. and Goldberg, M.D. (1981) Triplet and quadruplet pregnancies and management. *Obstet. Gynecol.*, **57**, 458–463.
- Schieve, L.A., Meikle, S.F., Ferre, C., Peterson, H.B., Jeng, G. and Wilcox, L.S. (2002) Low and very low birth weight in infants conceived with use of assisted reproductive technology. *New Engl. J. Med.*, **346**, 731–737.
- Seamark, R. F. and Robinson, J. S. (1995) Potential health problems stemming from assisted reproduction programmes. *Hum. Reprod.*, **10**, 1321–1322.
- Smith-Levitin, M., Kowalik, A., Birnholz, J., Skupski, D.W., Hutson, J.M., Chervenak, F.A. and Rosenwaks, Z. (1996) Selective reduction of multifetal pregnancies to twins improves outcome over nonreduced triplet gestation. *Am. J. Obstet. Gynecol.*, **175**, 878–882.
- Souter, I. and Murphy Goodwin, T. (1998) Decision making in multifetal pregnancy reduction for triplets. *Am. J. Perinatol.*, **15**, 63–71.
- Staessen, C., Nagy, Z.P., Liu, J., Janssenswillen, C., Camus, M., Devroey, P. and Van Steirteghem, A.C. (1995) One year's experience with elective transfer of two good quality embryos in the human in-vitro fertilization and intracytoplasmic sperm injection programmes. *Hum. Reprod.*, **10**, 3305–3312.
- Steer, C.V., Mills, C.L., Tan, S.L., Campbell, S. and Edwards, R.G. (1992) The cumulative embryo score: a predictive embryo scoring technique to select the optimal number of embryos to transfer in an in-vitro fertilization and embryo transfer programme. *Hum. Reprod.*, **7**, 117–119.
- Strandell, A., Bergh, C. and Lundin, K. (2002) Selection of patients suitable for one-embryo transfer may reduce the rate of multiple births by half without impairment of overall birth rates. *Hum. Reprod.*, **15**, 2520–2525.
- Strömberg, B., Dahlquist, G., Ericson, A., Finnström, O., Köster, M. and Stjernqvist, K. (2002) Neurological sequelae in children born after in-vitro fertilisation: a population-based study. *Lancet*, **359**, 461–465.
- Tarin, J.J. and Cano, A. (1995) Effects of manipulations *in vitro* of human oocytes and embryos on the birthweight of the resultant babies. *Hum. Reprod.*, **10**, 1322–1324.
- The Medical Research Council, the Natural Sciences and Engineering Research Council, and the Social Sciences and Humanities Research Council (1998) Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. <http://www.nserc.ca/programs/ethics/english/policy.htm>, Context of an ethics framework.
- Tiitinen, A., Halttunen, M., Harkki, P., Vuoristo, P. and Hyden-Granskog, C. (2001) Elective single embryo transfer: the value of cryopreservation. *Hum. Reprod.*, **16**, 1140–1144.
- Utsunomiya, T., Naitou, T. and Nagaki, M. (2002) A prospective trial of blastocyst culture and transfer. *Hum. Reprod.*, **17**, 1846–1851.
- Van Royen, E., Mangelschots, K., De Neubourg, D., Laureys, I., Ryckaert, G. and Gerris, J. (2001) Calculating the implantation potential of day 3 embryos in women younger than 38 years of age: a new model. *Hum. Reprod.*, **16**, 326–332.
- Van Royen, E., Mangelschots, K., De Neubourg, D., Valkenburg, M., Van de Meerse, M., Ryckaert, G., Eestermans, W. and Gerris, J. (1999) Characterization of a top quality embryo, a step towards single-embryo transfer. *Hum. Reprod.*, **14**, 2345–2349.
- Vilksa, S., Tiitinen, A., Hyden-Granskog, C. and Hovatta, O. (1999) Elective transfer of one embryo results in an acceptable pregnancy rate and eliminates the risk of multiple birth. *Hum. Reprod.*, **14**, 2392–2395.
- Visser, D.S. and Fourie, F.R. (1993) The applicability of the cumulative embryo score system for embryo selection and quality control in an in-vitro fertilization/embryo transfer programme. *Hum. Reprod.*, **8**, 1719–1722.
- White, G.B. and Leuthner, S.R. (2001) Infertility treatment and neonatal care: The ethical obligation to transcend specialty practice in the interest of reducing multiple birth. *J. Clin. Ethics*, **12**, 223–230.
- World Medical Association, I. Declaration of Helsinki. http://www.wma.net/e/policy/17-c_e.html.
- Yaron, Y., Bryant-Greenwood, P.K., Dave, N., Moldenhauer, J.S., Kramer, R.L., Johnson, M.P. and Evans, M.I. (1999) Multifetal pregnancy reductions for triplets to twins: comparison with nonreduced triplets and twins. *Am. J. Obstet. Gynecol.*, **180**, 1268–1271.