

Multiple gestation and infertility treatment: registration, reflection and reaction—the Belgian project

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Multiple pregnancies associated with infertility treatment are recognized as an adverse outcome and are responsible for morbidity and mortality related to prematurity and very low birthweight population. Due to the epidemic of iatrogenic multiple births, the incidence of maternal, perinatal and childhood morbidity and mortality has increased. This results in a hidden healthcare cost of infertility therapy and this may lead to social and political concern. Reducing the number of embryos transferred and the use of natural cycle IVF will surely decrease the number of multiple gestations. Consequently, optimized cryopreservation programmes will be essential. For non-IVF hormonal stimulation, responsible for more than one-third of all multiple pregnancies after infertility treatment, a strict ovarian stimulation protocol aiming at mono-ovulation is crucial. Multifetal pregnancy reduction is an effective method to reduce high order multiples but carries its own risk of medical and emotional complications. Excellent data collection of all infertility treatments is needed in our discussion with policy makers. The Belgian project, in which reimbursement of assisted reproduction technology-related laboratory activities is linked to a transfer policy aiming at substantial multiple pregnancy reduction, is a good example of cost-efficient health care through responsible, well considered clinical practice.

Key words: cost-effectiveness/infertility treatment/multiple pregnancies/policy

Introduction

The aim of infertility treatment is not to achieve a successful conception, but to offer the parents a healthy and normal child, a twin pregnancy being regarded as an adverse outcome (Land and Evers, 2003, report of an ESHRE consensus meeting). There is no doubt that the major complication of assisted reproductive technologies is the high incidence of multiple pregnancies, which is responsible for a substantial part of the cost and suffering (Callahan *et al.*, 1994; Bergh *et al.*, 1999b). Transferring multiple embryos into the uterus maximizes pregnancy rates, but yields an unacceptably high multiple pregnancy rate. Unfortunately, a high multiple pregnancy rate is not only associated with IVF and ICSI, but also with non-IVF procedures such as ovulation induction therapies, whether or not associated with intrauterine insemination (IUI).

The increasing availability of assisted reproduction technology during the past 20 years has received a lot of public attention not only because of the ethical implications, the inequities in access to infertility services and the issue of safety, but also because of the high cost associated with these treatments and the impact of age and multiple births on costs.

The most efficient way to reduce the huge cost associated with infertility treatment and the distress experienced by couples receiving assisted reproduction technology is the prevention of multiple pregnancies, not only the high order multiples (triplets, quadruplets, etc.), but even more importantly the reduction of twin pregnancies. For IVF and ICSI, due to the improving insights into embryo quality assessments, elective single embryo transfer (eSET) could be the method of choice, especially in the good prognosis group (Gerris *et al.*, 1999; Van Royen *et al.*, 1999).

On July 1, 2003, the Belgian government started with the reimbursement of IVF/ICSI laboratory costs of couples with female age <43 years for a maximum of six treatment cycles in a lifetime. This strategy was only acceptable and affordable if the number of embryos transferred was limited, subsequently leading to a decrease in perinatal costs associated with multiple pregnancies. This project to meet the needs of most subfertile couples without additional costs was prepared by a group of Belgian opinion leaders in the field of assisted reproductive technology and was agreed by the government. In this way, a win–win situation for both the patients and the government was feasible.

Multiple pregnancies following infertility treatment: the current situation

In most developed countries, 30–50% of all twin pregnancies result from infertility treatment. Data for England and Wales show that between 1975 and 1994 the twin maternity rate increased by 35% and the triplet and high order multiple pregnancy rate has more than trebled, as a consequence of increased use of ovulation induction and multi-embryo transfer in the treatment of subfertility (Dunn and MacFarlane, 1997). Pressure to achieve higher pregnancy rates in infertility treatment has resulted in an unacceptably high multiple pregnancy rate in many countries. In the USA, multiple births occurred after 39% of IVF cycles (ASRM/SART, 2000, 2002a,b; Katz *et al.*, 2002). The ESHRE reported a figure between 26.3 and 29.1% based on European data on assisted reproduction technology from 1997, 1998 and 1999 (Nygren and Andersen, 2001a, b, 2002). Of all infants born after IVF and/or ICSI in 1998, only 57.3% were born as singletons; 37.1% were born as twins and 5.6% as triplets or quadruplets.

Controlled ovarian stimulation (COS), with or without IUI or TC (timed coitus), is often used and generally accepted as a valuable first line treatment in cases of subfertility due to ovulatory disorders, unexplained infertility and moderate male factor subfertility (Peterson *et al.*, 1994; Ombelet *et al.*, 1995; Voorhis *et al.*, 1997, 1998; Zayed *et al.*, 1997; Guzick *et al.*, 1998; Van Karande *et al.*, 1999; Cohlen *et al.*, 2000; Daya, 2000; Goverde *et al.*, 2000; Philips *et al.*, 2000; Van Voorhis and Syrup, 2000; Homburg and Insler, 2002; Hughes, 2003). Because of the widespread use of gonadotrophins, induction of ovulation, with or without IUI, has become the main cause of multiple pregnancies related to infertility treatment in the USA (Evans *et al.*, 1995; Gleicher *et al.*, 2000; Tur *et al.*, 2001).

To investigate the importance of non-IVF ovarian stimulation on the incidence of multiple pregnancies in Flanders, we studied the data from the 'Studiecentrum voor Perinatale Epidemiologie' (SPE). The SPE prospectively collects data on the medical and obstetric history, and on perinatal events of each hospital delivery in Flanders of >21 weeks of gestational age and ≥ 500 g at birth. Full cooperation of all 80 departments of obstetrics in Flanders has been established since 1991. The data are based on questionnaires completed by obstetricians and paediatricians in the early neonatal period. All data are sent to a central data coordinator, who cleans the data for errors and omissions before entering in the database. Subsequently the files are stored onto a computer database. Each year a complete analysis of these data is performed and published in a yearly global report and a unique report per obstetric unit.

A retrospective analysis of 547 197 deliveries between 1993 and 2002 showed that infertility treatment with ovarian stimulation, including IVF- and non-IVF procedures, was responsible for 4.6% of all registered deliveries (26 656/547 197). Multiple pregnancies as a result of infertility treatment were observed in 1.54% of all deliveries ($n = 8895$). Of all singletons, twins and triplets respectively 3.2, 38.1 and 79.6% resulted from hormonal stimulation. Of all multiple pregnancies following ovarian stimulation, IVF/ICSI was performed in 66.7%, COS with timed coitus (COS-TC) in 23.7% and COS-IUI in 9.6% of cases. This may be explained by the fact that most centres in Flanders

use clomiphene citrate rather than gonadotrophins in IUI (W.Ombelet 2003, unpublished data, questionnaire of the Flemish Society of Obstetrics and Gynaecology). Concerning the different treatment procedures, the multiple birth rate was 27.2% for IVF, 25.7% for ICSI, 13.7% for COS-IUI and 9.7% for COS-TC respectively.

Access to assisted reproduction services and infertility treatment

Subfertile people all over the world desire to give birth to a healthy child. It was noted in the UN Declaration of Human Rights, Article 16.1: 'Men and women of full age, without any limitation due to race, nationality or religion, have the right to marry and found a family'. However, social pressure to have children, access to assisted reproduction technology units and the number of assisted reproduction technology treatment cycles per head of population varies from country to country. The assumed need for IVF/ICSI services was examined by the ESHRE Capri workshop group (2003). The (under)estimated need for assisted reproduction technology was 1500 cycles per annum per million population. This means that in the majority of countries, the uptake and availability of IVF falls short of this estimated minimum. To a large extent, this can be explained by the high cost of a single IVF cycle in most countries (Fauser *et al.*, 2002).

It has been reported that the use of assisted reproduction technology is greater in countries that subsidize expenses, such as The Netherlands, Scandinavian countries and France (Katz *et al.*, 2002). In many countries, basic fertility services are provided through public funding, whereas IVF provision is limited or absent (Hughes and Giacomini, 2001). Insurance coverage for IVF services seems to be associated with increased utilization of IVF and with a decreasing number of embryos transferred (Reynolds *et al.*, 2003). Whether this translates into decreased multiple birth risk is less clear. Even in US states that require insurance coverage for IVF, the rate of multifetal pregnancy is still much too high (Neumann, 1997; Jain *et al.*, 2002; Guzick, 2002; Reynolds *et al.*, 2003).

The risks of multiple pregnancies

Multiple pregnancy is the most important adverse outcome in current methods of infertility treatment and the rationale for reducing multiple births is obvious: not only neonatal complications and their long term sequelae, but also maternal complications and social problems are seen more often after multiple birth (Elster, 2000; Denton and Bryan, 2002; Finnstrom, 2002; Ozturk and Templeton, 2002; Bryan, 2003a,b).

Maternal complications

Many pregnancy symptoms are increased with multiple gestation. Maternal complications include a significant increase in anaemia. Multiple pregnancies are predisposed to a higher incidence of iron and folate deficiency anaemia due to a higher fetal demand for nutritional precursors combined with the dilutional effect of the increased maternal plasma volume (Albrecht and Tomich, 1996; Malone *et al.*, 1998). Compared to singletons,

the risk of pregnancy-induced hypertension (PIH) and pre-eclampsia in twins is reported to be 5- and 10-fold higher in primigravidae and multigravidae respectively (MacGillivray and Campbell, 1988). For triplet pregnancies, Malone *et al.* (1998) described an incidence of 24, 9 and 2% for severe pre-eclampsia, HELLP syndrome and eclampsia respectively.

Polyhydramnios is observed more frequently in multiple pregnancies and may be present in up to 12% of multiple pregnancies (Keith *et al.*, 1980).

The prevalence of gestational diabetes is associated with the number of fetuses: 3% for singleton pregnancies, 5–8% for twins and >10% for triplets (Seoud *et al.*, 1992; Malone *et al.*, 1998; Ozturk and Templeton, 2002).

Dystocia and a high Caesarean section rate will contribute to the excess maternal morbidity. In a retrospective analysis of 562 921 deliveries in Flanders over a 10 year period (1993–2002), the risk of an operative delivery was 20.4 and 86.6% for twin and triplet pregnancies compared to an overall incidence of 14.4% for all deliveries during the same study period (SPE data, 2003).

Postnatal problems such as social isolation, depressive illnesses and child abuse are also more commonly observed after multiple pregnancies, especially in case of preterm birth (Albrecht and Tomich, 1996; Garel *et al.*, 1997; Bryan, 2003b). Even an increased maternal mortality rate for multiple pregnancies compared to singletons is reported in Europe (10.2–14.9 versus 4.4–5.2 per 100 000 pregnancies) (Senat *et al.*, 1998) and Latin America (77 versus 43 per 100 000 pregnancies) (Conde-Agudelo *et al.*, 2000).

Perinatal data

Many multiple births are low birthweight (LBW, <2500 g), very low birthweight (VLBW, <1500) or extremely low birthweight (ELBW, <1000 g), conditions that magnify both short-term and long-term risks. Compared to singletons, twins and triplets have post-neonatal survivors' relative risks for severe handicap of 1.7 and 2.9 respectively (Luke and Keith, 1992). Twins and triplets also have an increased relative risk for infant mortality of 6.6 and 19.4 respectively. Although twin pregnancies following IVF/ICSI are more likely to result in discordant birthweight infants, the perinatal outcome is similar to that of spontaneously conceived twin pregnancies (Bernasko *et al.*, 1997; Dhont *et al.*, 1999; Koudstaal *et al.*, 2000; Kozinszky *et al.*, 2003; Pinborg *et al.*, 2003; Zaib-un-Nisa *et al.*, 2003; Helmerhorst *et al.*, 2004).

Congenital malformations unique to multiple pregnancies are infrequent and related to monochorionic placentation: twin–twin transfusion syndrome, twin reversed arterial perfusion sequence and conjoined twins. In a Swedish IVF population, the frequency of congenital malformations was 4.7% among singletons and 6.3% among twins, compared to 3.9% in the general population (Ericson and Källén, 2001). Major malformations were found more often after multiple gestation in a large series of 5795 IVF and ICSI children reported by Bonduelle (2003). When matched for maternal age and parity, Dhont *et al.* (1999) were unable to demonstrate a significant increase of congenital malformations in twin pregnancies after assisted reproductive technology compared to naturally conceived twin pregnancies. In a large retrospective cohort study in Sweden, assisted reproductive

technology twins and control twins did not differ regarding the prevalence of malformations (Bergh *et al.*, 1999b).

Low birthweight and pre-term delivery are the most important factors accounting for the excess in perinatal mortality (PNM) and morbidity in multiple pregnancies compared to singletons. For twin pregnancies, the outcome is mainly determined by chorionicity, rather than zygosity (Sebire *et al.*, 1997). Monochorionic twins carry the highest risk of a poor outcome. Approximately 20% of all twins are monochorionic. The proportion is higher in spontaneous twins (30%) compared to assisted reproduction twins (3.7%) (Derom *et al.*, 2001).

In our SPE data on 26 656 assisted reproduction pregnancies in Flanders, we observed a PNM of 10, 27 and 62 per 1000 total births for singletons, twins and triplets respectively. As the number of fetuses increases, the duration of gestation decreases with a mean of 3 weeks per additional fetus (Table I). Preterm delivery occurred in 95.9% of triplet pregnancies (mean gestational age 32.7 weeks) and 53.8% of twin deliveries (mean gestational age 35.6 weeks). The incidence of early preterm delivery (<32 weeks) was 5-fold higher in twin pregnancies and 17-fold higher in triplet pregnancies compared to singletons following hormonal stimulation. VLBW (<1500 g) occur respectively 5- and 17-fold more often in twin and triplet pregnancies (Table I). Our results are very similar to the US data presented by Keith and Oleszczuk (1999) describing the gestational age and birthweight characteristics of 3 603 971 singletons, 463 856 twins and 18 843 triplets, all US residents. Comparable figures were also reported by Martin *et al.* (2002).

In our series of 26 656 assisted reproductive technology deliveries, neonatal morbidity was significantly increased for

Table I. Perinatal outcome of 26 656 children born after ovulation induction (IVF and non-IVF) (Studiecentrum voor Perinatale Epidemiologie data on 574 197 deliveries in Flanders between 1993 and 2002)

Population characteristics	Singletons No. (%)	Twins No. (%)	Triplets No. (%)
Deliveries	17761	4047	270 ^a
Gestational age at delivery			
< 32 weeks	266 (1.5)	314 (7.8)	69 (25.5)
32–36 weeks	1357 (7.6)	1863 (46.0)	190 (70.4)
≥ 37 weeks	16 138 (90.9)	1870 (46.2)	11 (4.1)
Children born (>500 g)	17 761	8094	799 ^a
Birthweight (g)			
500–999	137 (0.8)	254 (3.1)	80 (10.0)
1000–1499	153 (0.9)	388 (4.8)	152 (19.0)
1500–2499	1089 (6.1)	3905 (48.2)	510 (63.8)
≥ 2500	16 382 (92.3)	3549 (43.8)	57 (7.1)
Congenital malformations	354 (2.0)	246 (3.0)	28 (3.5)
Perinatal mortality	176 (1.0)	225 (2.8)	50 (6.2)
Neonatal morbidity			
Endotracheal ventilation	329 (1.8)	612 (7.5)	177 (22.1)
Intracranial bleeding	84 (0.4)	160 (1.9)	45 (5.6)
Respiratory distress syndrome	284 (1.6)	650 (8.0)	163 (20.4)

Values in parentheses are percentages.

For all studied parameters, differences between singletons and twins or triplets were statistically significant ($P < 0.01$).

^aThe discrepancy between the number of deliveries and children born in triplet pregnancies can be explained by the fact that not all members of a triplet pregnancy have a birthweight of >500 g and therefore some of these births were not registered.

multiples compared to singletons. We observed an increased incidence of congenital malformations and a higher incidence of intraventricular haemorrhage, ventilatory support and respiratory distress syndrome (Table I).

Childhood data

Even if infants from multiple pregnancies survive the early post-natal period, they continue to have an increased risk for long-term developmental and physical disabilities.

The risk of handicap increases with the number of fetuses and at least one handicapped child is found in 7.4, 21.6 and 50% for twin, triplet and quadruplet pregnancies respectively (Yokoyama *et al.*, 1995). Luke and Keith (1992) reported a higher relative risk for severe and moderate handicap of 1.7 and 1.3 for twins compared to singletons. For triplets this relative risk for severe and moderate handicap rises to 2.9 and 1.7 respectively.

Limited information is available on the long-term neurological sequelae of prematurity and multiple gestation, and most studies report on small series. Cerebral palsy is one of the most important neurological impairments associated with premature birth and multiple pregnancy and has been reported to occur respectively 5–6 and 17–20 times more often in twin and triplet pregnancies compared to singletons (Pettersson *et al.*, 1993; Pharoah and Cooke, 1996).

Many studies have proven that severe disability is common among children born as extremely premature infants (Nishida, 1993; Piecuch *et al.*, 1997; Tin *et al.*, 1997; Wood *et al.*, 2000, 2003; Campbell and Fleischman, 2001; Bracewell and Marlow, 2002; Anderson and Doyle, 2003). Up to 45% of VLBW infants show abnormal test score patterns for intellectual status, suggesting specific intellectual problems at the age of 8–11 years (Nishida, 1993; Hunt *et al.*, 1988).

On the other hand, multiple pregnancy as such seems to be of no predictive value in predicting the risk for long-term developmental disabilities. For children born prematurely, there is no tendency for singletons to do better than multiples (Nielsen *et al.*, 1997; Miyahara *et al.*, 2003).

The costs of multiple pregnancies

Assisted reproductive technology accounts for 0.08–0.16% of the total health care costs in the Nordic countries (Granberg *et al.*, 1998), while in the USA expenses for infertility, including IVF, account for 0.4–0.8% of these costs (Griffin and Panak, 1998; Stovall *et al.*, 1999). According to Collins (2001), the median projected cost per IVF cycle and per delivery is US\$9226 and US\$56419 in the USA compared to US\$3531 and US\$20522 in 25 other countries. The costs of IVF/ICSI to individual couples range from 10% of annual household expenditures in European countries to 25% in Canada and the USA (Collins, 2002).

Costs linked to infertility treatment include the cost of the treatment procedures and the cost for health care of the pregnant women and their offspring, taking into account the savings from reduced utilization of alternative treatments (Collins *et al.*, 1995; Laufer *et al.*, 1995; Goldfarb *et al.*, 1996; Wolner-Hansen and Rydhstroem, 1998; Collins and Graves, 2000).

The different factors that influence the higher cost of multiple pregnancies compared to singletons is shown in Figure 1. Even when couples themselves are paying for the assisted reproduction procedures, the care for their offspring remains a burden on the community if neonatal, paediatric, social and educational services are financed by public funds.

In terms of absolute figures and because of their higher incidence, twin pregnancies outweigh by far the effect of high order multiple pregnancies (Dhont, 2001). Moreover, it has been proven that the transfer of a single embryo after IVF and/or ICSI is at least as successful and cost-efficient as the transfer of two embryos (Wolner-Hansen and Rydhstroem, 1998; De Sutter *et al.*, 2002; Gerris *et al.*, 2004). This finding is very important, particularly as these studies did not take into account the additional costs of long-term handicaps due to extreme prematurity.

The higher health care expenses of multiple births compared to singletons is mainly caused by the higher costs of obstetric care, neonatal intensive care cost and costs linked to childhood disabilities. The cost of obstetric care of a multiple pregnancy is increased in terms of medication used, hospital stay, extra investigations and the likelihood of operative delivery. The obstetric care costs are 2.1-, 4.5- and 7-fold greater for twins, triplets and quadruplets compared to singletons (Mugford and Henderson, 1995). Preterm birth is a major predictor of how much an individual will cost the community during its first 5 years of life (Petrou *et al.*, 2003). Petrou (2003) reviewed the literature on the economic impact in terms of neonatal care hospital costs of preterm birth and low birthweight newborns. In the US the costs for ELBW (<1000 g) and VLBW (1000–1499) was £39483 and £22541 respectively. Outside the USA the figures were £29757 and £14986 respectively.

But even after the neonatal period, the burden on the health care budget continues. Premature and/or low birthweight babies are more likely to have special needs, ongoing paediatric care and other therapies as well as special education. For a low birthweight child, the average cost of health care and education up to the age of 8 years is 17-fold greater compared to a normal birthweight child (Stevenson *et al.*, 1996a,b). Garceau *et al.* (2002) reviewed all published health-economic studies performed in the field of assisted reproduction. They concluded that the quality of most studies is poor and that more robust studies were needed; the indirect and long-term costs especially were not sufficiently accounted for in the available studies.

Preventive measures

The risk of multiple pregnancy after IVF is related to the fertilization rate, the mean number of embryos obtained in relation to the number of oocytes retrieved, the number of embryos transferred, the embryo quality and cumulative or average embryo score (Templeton and Morris, 1998; Devreker *et al.*, 1999; Van Royen *et al.*, 1999; Salha *et al.*, 2000; Strandell *et al.*, 2000; Lundqvist *et al.*, 2001). The indication for IVF, except for the pure male factor, and the rank of attempt show no relationship with the multiple pregnancy rate after assisted reproduction (Templeton *et al.*, 1996; Cohen, 2003). The most important factor is undoubtedly the number of embryos transferred. After the transfer of three, four and five embryos the incidence of triplet pregnancies is respectively 8, 11 and 15% (FIVNAT, 1995; Cohen, 2003).

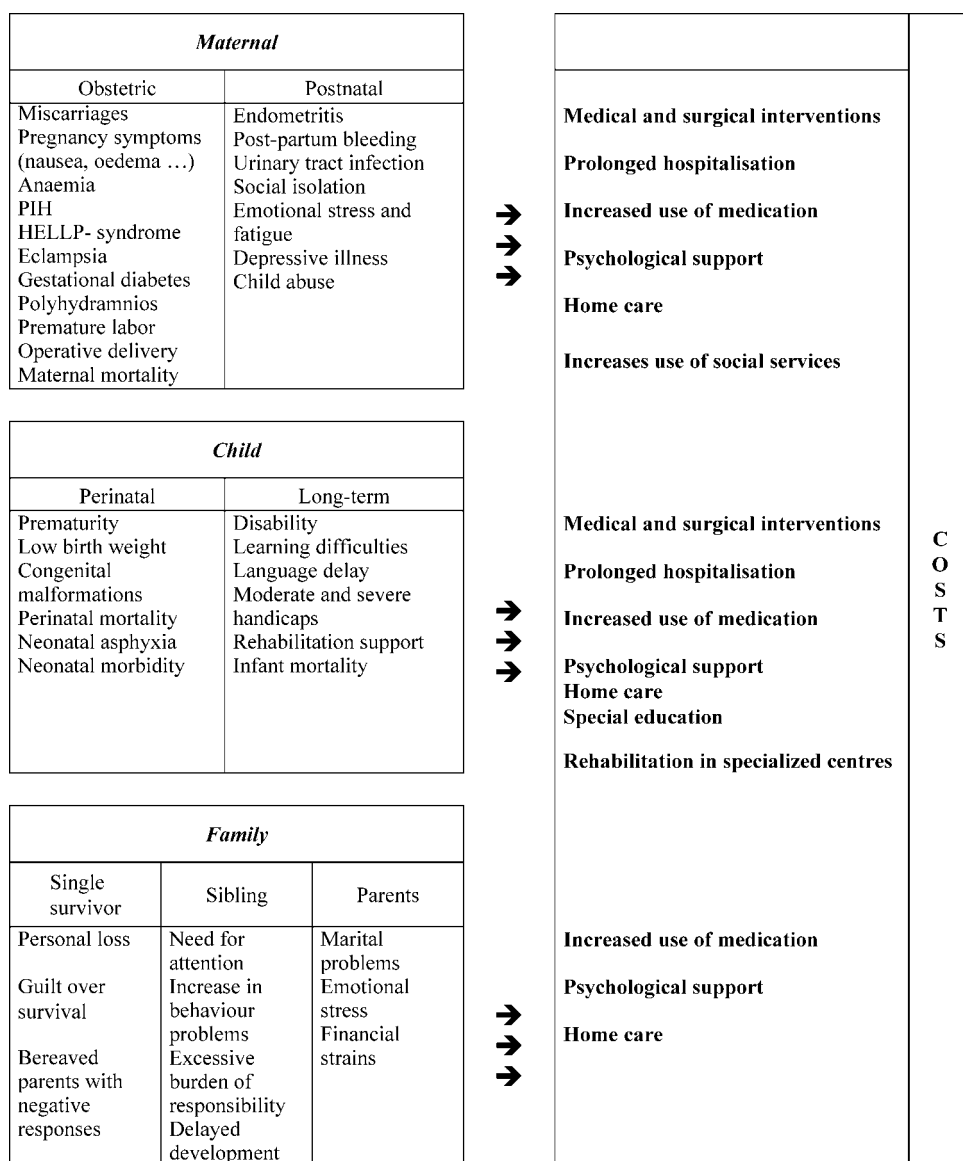


Figure 1. Different factors that influence the higher cost of multiple pregnancies compared to singletons. PIH = pregnancy induced hypertension. HELLP = hemolysis, elevated liver enzymes, low platelets.

Reduction of embryos transferred

Reports on IVF in natural cycles are limited and the results are not consistent (Fahy *et al.*, 1995; Feldman *et al.*, 2001; Nargund *et al.*, 2001; Omland *et al.*, 2001; Bauman *et al.*, 2002; Pelinck *et al.*, 2002).

Nowadays, a policy of eSET in stimulated cycles seems to be the most efficacious measure to reduce the incidence of twin pregnancies (Wolner-Hanssen and Rydhstroem, 1998; Gerris *et al.*, 1999; Van Royen *et al.*, 1999; Gerris and Van Royen, 2000; Dhont, 2001; Martikainen *et al.*, 2001; Tiitinen *et al.*, 2001, 2003; De Sutter *et al.*, 2003). In a large retrospective study it was shown that, with the implementation of elective SET, multiple pregnancy delivery rates could drop from 25 to 5% (Tiitinen *et al.*, 2003). Elective SET would result in an acceptable ongoing pregnancy rate if at least one ‘top quality’ embryo is available (Gerris *et al.*, 1999; Van Royen *et al.*, 1999; Martikainen *et al.*, 2001).

To obtain satisfying results, the efficacy of embryo scoring will be crucial. Various scoring systems throughout preimplantation development are important in identifying the most viable embryo for transfer. Pronuclear morphology, embryo development rate, fragmentation, blastomere multinucleation, development to blastocyst and preimplantation genetic diagnosis (PGD) can be helpful in achieving the ultimate goal: an acceptable pregnancy rate after eSET associated with a very low multiple gestation rate (Shoukir *et al.*, 1997; Munné *et al.*, 1999; Tesarik and Greco, 1999; Van Royen *et al.*, 1999; Magli *et al.*, 2001; Gianaroli *et al.*, 1999; Gianaroli, 2003; Gardner, 2003). On the other hand, it seems that women who received embryos originating from oocytes developed in well-vascularized follicles had a statistically higher pregnancy rate than women who received embryos deriving from oocytes grown in more poorly vascularized follicles (Chui *et al.*, 1997; Van Blerkom *et al.*, 1997; Van Blerkom, 1998, 2000; Bhal *et al.*, 1999; Huey *et al.*, 1999; Borini *et al.*, 2001).

In Belgium a steady, decline was observed in the number of embryos transferred since 1996. The proportion of deliveries of multiples after assisted reproductive technology has also decreased from 34% in 1996 to 24% in 2001. In particular, the introduction of eSET in a few large infertility centres since 1998 has accelerated this development (Gerris *et al.*, 1999; Dhont, 2001; De Sutter *et al.*, 2002). eSET was performed in 14% of all transfers in Belgium in 2001 and this number is increasing each year (Figure 2a,b). This strategy has not affected the overall national results: the ongoing pregnancy rate per transfer has always fluctuated by ~20% for the last 10 years and remained 22% in 2001. If eSET was performed (when more than one embryo was available for transfer), this led to an ongoing pregnancy rate per transfer of 19%, compared to 26% for elective double embryo transfer (DET). After triple embryo transfer, this figure is only 23%, which is explained by the fact that in Belgium nowadays three embryos are only transferred in poor prognosis cases.

The role of cryopreservation

With a strategy of transferring fewer embryos, methods of cryopreservation and replacement should be optimized (Cohen and

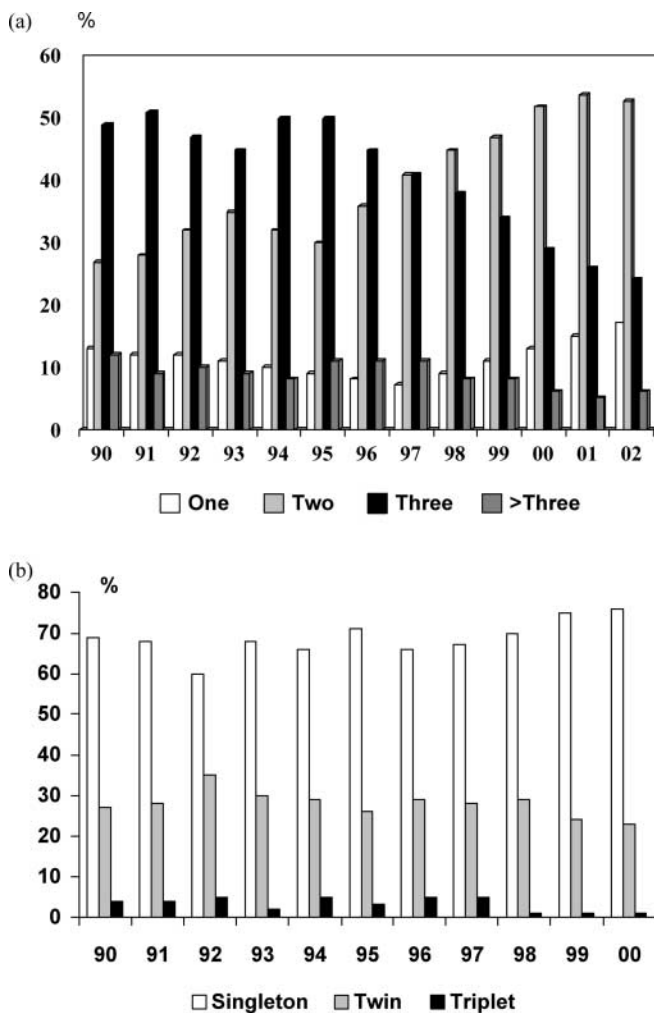


Figure 2. (a) Belgian register for assisted procreation (BELRAP) 1990–2002: number of embryos transferred. (b) BELRAP 1990–2000: number of babies delivered

Jones, 2001; Gerris *et al.*, 2003; Veeck and Rozenwaks, 2003). Scandinavian reports have shown that in cases where more than one embryo was available for transfer and eSET was performed in the first fresh cycle, the cumulative pregnancy rate after frozen–thawed embryo transfer was >47% (Vilksa *et al.*, 1999; Martkainen *et al.*, 2001; Tiitinen *et al.*, 2001). Proper counselling on the risks of twin pregnancies and explaining the good results obtained with eSET combined with frozen–thawed embryo transfer could easily convince most couples to accept this novel strategy (Schnorr *et al.*, 2001; Tiitinen *et al.*, 2003).

Non-IVF and ovarian stimulation

The available data in the literature suggest that non-IVF ovarian stimulation is responsible for at least one-third of multiple pregnancies (Bergh *et al.*, 1999b; Tur *et al.*, 2001). In COS, with or without IUI, the prediction of multiple gestation is highly uncertain especially when gonadotrophins are used (Gleicher *et al.*, 2000). Cancellation of the insemination procedure, rescue IVF with or without the use of GnRH antagonist and follicular aspiration are reasonable options when three or more follicles of ≥15 diameter are present (Lessing *et al.*, 1991; Many *et al.*, 1999; Fatemi *et al.*, 2002). Transvaginal ultrasound-guided aspiration of supernumerary ovarian follicles increases both the efficacy and the safety of COS-IUI with gonadotrophins (De Geyter *et al.*, 1998; Albano *et al.*, 2001). This method represents an alternative for conversion of overstimulated cycles to rescue IVF.

Exogenous pulsatile GnRH can be used for anovulatory patients with hypogonadotropic hypogonadism which restores normal gonadotrophin secretion, and, if pregnancy occurs, the multiple pregnancy rate is not increased. In obese patients with normogonadotrophic chronic anovulation [World Health Organization (WHO) group II], a diet and exercise can be recommended before any other interventions are considered. Ovulation induction can be achieved with clomiphene citrate, a good first line option since ovulation can be induced in ~50–70% of cases, with a multiple pregnancy rate of 6–8% (Ombelet *et al.*, 1996, 1997; Sovino *et al.*, 2002).

Gonadotrophins are necessary in clomiphene-resistant cases and yield better pregnancy rates compared to clomiphene citrate, but at the expense of a higher multiple pregnancy rate of >15% in most reports (Ombelet *et al.*, 1996; Fauser and Van Heusden, 1997; Guzick *et al.*, 1998, 1999; Pasqualotto *et al.*, 1999; Tur *et al.*, 2001). Low dosage gonadotrophin protocols are being tested, resulting in a lower multiple birth rate without influencing the ongoing pregnancy rate too much (Dhaliwal *et al.*, 2002). Alsina *et al.* (2003) published the results of low dose recombinant FSH for ovulation induction in 945 cycles: low dose regimen of 50 IU of recombinant FSH was efficient, safe and well tolerated for inducing follicular development in WHO group II anovulatory women. The cumulative pregnancy rate was 53.1% with a 14.4% pregnancy rate per cycle. Most interesting was the low multiple pregnancy rate (only 5.9%).

For anovulatory women with polycystic ovarian syndrome (PCOS), the use of insulin-sensitizing drugs such as metformin is another attractive therapeutic option. Metformin appears to ameliorate the biochemical profile and improve reproductive function. On the other hand, administration is simple, hypoglycaemia

rare and weight loss promoted (McCarthy *et al.*, 2004). For the treatment of anovulatory infertility caused by PCOS, metformin plus clomiphene seems to be more effective than clomiphene alone in inducing ovulation. In obese women, metformin plus a low calorie diet may be associated with more weight loss than a low calorie diet alone (Barbieri, 2003). Two reviews examined the effectiveness and role of metformin in the treatment of PCOS anovulatory infertility and came to the conclusion that more well-designed prospective randomized controlled trials with the primary end point of pregnancy or live birth rate are still required (Costello and Eden, 2003; Haas *et al.*, 2003). In a prospective study, Malkawi *et al.* (2003) concluded that clomiphene-resistant patients with PCOS can be treated effectively either by metformin or by laparoscopic ovarian drilling.

Indeed, laparoscopic or transvaginal ovarian diathermy might be another effective treatment option in anovulatory PCO patients (Farquhar *et al.*, 2002; Casa *et al.*, 2003). According to a Cochrane review however, there is insufficient evidence to determine a difference in ovulation or pregnancy rates of ovarian surgery compared to gonadotrophin therapy as a secondary treatment for clomiphene-resistant women. However, multiple pregnancy rates were low and comparable to natural conception in those women who conceived following laparoscopic ovarian drilling (Farquhar *et al.*, 2000).

Multifetal pregnancy reduction

Multifetal pregnancy reduction (MPR) was introduced by Aberg *et al.* (1978) to selectively eliminate a fetus affected by a genetic disorder in a twin pregnancy. Nowadays, multifetal reduction is also carried out to improve the chances of survival and health of the remaining fetus(es) in twin and high order multiple pregnancies.

Multifetal reductions are performed either transabdominally or transvaginally between 10 and 13 weeks of gestation. Operator skills are important due to a lengthy learning curve (Evans *et al.*, 1995, 2001). MPR in triplet and high order multiple pregnancy increases survival rates and lessens obstetric complications at the expense of a small pregnancy loss rate (Yaron *et al.*, 1999; Berkowitz, 2003; De Catte, 2003; Dodd and Crowther, 2004). Reduction of triplet pregnancies to twins increases gestation by 2–3 weeks, and reduction to twins from higher order multiplets

prolongs the duration of gestation even more (Stone *et al.*, 2002; Rochon and Stone, 2003).

It is very important that the couples should receive all the information on the expected outcome before making the decision. Women who have undergone MPR experience some feelings of sadness and guilt following the procedure, but almost all couples were convinced that high-order pregnancies should be avoided (Garel *et al.*, 1997; Bergh *et al.*, 1999a).

Need for data collection

Official statements on reimbursement of assisted reproduction services and guidelines on the prevention of multiple pregnancies can be expected in the near future in many countries. Data collection regarding fertility treatment and their outcomes per centre will be of extreme importance and should be integrated into statutory regulations and national guidelines in order to fit the bill (Templeton, 2003).

IVF registration has been done in many countries for many years. Registration of non-IVF hormonal treatment procedures, with or without IUI, is lacking and should be started as soon as possible. As mentioned before, non-IVF is responsible for 35–50% of all assisted reproduction multiple pregnancies (Bergh *et al.*, 1999b; Tur *et al.*, 2001).

In Belgium, almost all IVF/ICSI cycles have been registered since 1991 (Belgian Register for Assisted Procreation). Perinatal data for all deliveries in Flanders (>50% of all deliveries in Belgium) have been available since 1988 (SPE data, described above). Detailed data of the neonatal period are also available for all Belgian newborns admitted in a neonatal intensive care unit. With all these data, it was much easier to argue with the government for the reimbursement of infertility treatment procedures and stipulate evidence-based guidelines for assisted reproduction practice.

The Belgian project

Until 2002, ~50–75% of the medical costs of assisted reproductive technologies were reimbursed by the national health care system. These costs included the medication used, the visits and the costs for monitoring (ultrasonography, hormonal assays).

Woman ≤ 35 years old	
1st attempt	⇒ single embryo transfer (SET)
2nd attempt	⇒ single embryo transfer (SET) if one or more top-embryos are available ⇒ transfer of two embryos if no top embryo is available
3rd–6th attempt:	⇒ maximum two embryos transferred
Women > 35 and ≤ 39 years old	
1st and 2nd attempt	⇒ maximum two embryos transferred
3rd – 6th attempt:	⇒ maximum three embryos transferred
Women > 39 and ≤ 42 years old	
1st – 6th attempt	⇒ no limit for number of embryos transferred

Figure 3. Reducing the multiple pregnancy rate in IVF-related procedures using fresh embryos: the Belgian strategy.

There was no reimbursement for the laboratory costs, neither for IVF/ICSI nor for IUI. On average, couples had to pay €200, €1000 and €1250 respectively for IUI, IVF and IVF/ICSI.

In 2001 the Belgian government decided to change this reimbursement policy for IVF-related procedures. It was mentioned from the start that financial resources were limited and consequently a certain inventiveness was called for.

Therefore, the Belgian College of Physicians in Reproductive Medicine, in cooperation with the Belgian Society for Reproductive Medicine (BSRM) and all licensed IVF centres, agreed on a proposal to the government in which reimbursement of IVF and ICSI treatment cycles would be linked to a 50% reduction of twin pregnancies, subsequently minimizing the risks for high order multiple pregnancies to almost zero. This proposal was influenced by our own BELRAP (Belgian Register for Assisted Procreation) registration figures and based on a reduction of embryos transferred after assisted reproductive technology, considering the possible influence of female age and cycle

number on the incidence of multiple pregnancies. It was expected that couples would agree to SET if reimbursement could be offered for all laboratory activities. A working group of expert embryologists was asked to calculate the real laboratory cost for IVF/ICSI. The cost calculation was based on the main expense factors for personnel, equipment, laboratory supplies and hospital building accommodation for a medium-sized IVF unit. It was concluded that €1182 was a fair estimate of the reimbursement fee per IVF/ICSI cycle.

Figure 3 shows the protocol that was suggested to and agreed upon by the government in order to reduce high order multiple pregnancies significantly and to decrease the number of twin pregnancies by 50% within 1 year of implementation. In this new strategy, up to six cycles in a lifetime are reimbursed for all assisted reproduction-related laboratory activities.

By reducing the twin pregnancy rate by 50% and the high order multiples to almost zero, neonatal costs linked to multiple pregnancy were also reduced by >60% (Figure 4a) when compared to the reference year 1997 (before a trend to SET and DET was observed in our BELRAP data). The government decided to reimburse a maximum of 7000 assisted reproduction cycles per year (€1182 per cycle). This means a total cost of 8 270 000 per year. Considering the fact that 70% of twins and triplets are admitted to the NIC (neonatal intensive care unit) with a mean cost of €12 500, 87.6% of the reimbursement funds can be saved by reducing the neonatal costs alone. Taking into account that this strategy should result each year in 35 fewer children with a severe handicap (3.7% of twins and 7.2% of triplets) due to extreme prematurity and dysmaturity (mean lifetime cost for a severely handicapped child is between €1.5 and €2 million), this project is also unique from a health-economic point of view (Figure 4b) (Nishida, 1993; Yokoyama *et al.*, 1995).

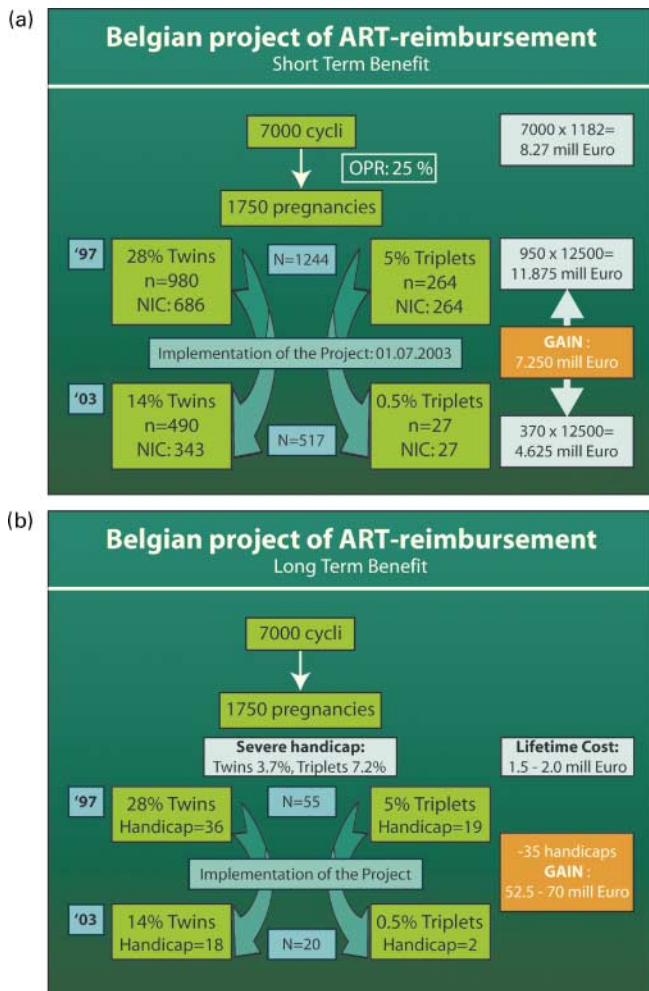


Figure 4. (a) Belgian project of assisted reproduction reimbursement: short-term benefit considering that 70% of twins and 100% of triplets are admitted to the neonatal intensive care with a mean estimated cost of €12 500 per baby. OPR = ongoing pregnancy rate. (b) Belgian project of assisted reproduction reimbursement: long-term benefit considering that 3.7% of twins and 7.2% of triplets are severely handicapped with major neurological or developmental disability. (Yokoyama *et al.*, 1995) with a mean lifetime cost of €1.5–2.0 million per baby (Nishida, 1993).

Conclusion

Multiple gestation is now recognized as a major adverse event of infertility treatment. Maternal and perinatal morbidity and mortality rates are significantly increased compared to singleton pregnancies. In an era of health cost awareness, excellent data collection and presentation is essential to enter discussion with budgetary policy-makers.

The reduction of embryos transferred in assisted reproductive technology, together with a careful and well-considered management of non-IVF ovarian stimulation, will finally result in a higher proportion of less complicated and therefore less expensive singleton pregnancies—the ultimate goal of infertility treatment. When carefully audited, managed fertility treatment could serve the needs of the majority of subfertile couples being affordable to the community at the same time.

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