

## **Ethical Aspects of Multiple Pregnancy**

Jacques Milliez, M.D.<sup>1\*</sup>, Bernard Dickens, M.D.<sup>2</sup>

1. Hospital Saint Antoine, Paris, France

2. Faculty of Law, University of Toronto, Toronto, Canada

### **Abstract**

The rate of multiple pregnancy has dramatically increased during the past decades, along with the diffusion of assisted reproduction technology (ART). Multiple pregnancy entail an increased risk of, at times life threatening, maternal complications i.e. pre-eclampsia, eclampsia or abruptio placenta, of serious neonatal hazards, i.e. extreme prematurity or growth retardation, as well as deleterious impact on family and social life. It raises the ethical debate of fetal reduction. The international federation of gynaecologists and obstetricians (FIGO) recommendations on iatrogenic multiple pregnancy emphasizes the need for the transfer of a limited number of embryos during ART in order to secure a singleton pregnancy.

**Keywords:** Iatrogenic Multiple Pregnancy, Maternal and Neonatal Hazards, Embryo Reduction

### **Introduction**

The rate of multiple pregnancy has dramatically increased since the early seventies. Twin delivery steadily increased from 8.9 per thousand live births in 1972 to 14.4 per thousand live births in 1998. Triplet pregnancy in the mean time increased from 0.9 to 4.5 per thousand live births (1). In England, Wales, United States twin pregnancy increased by 62% during the past thirty years, whereas triplet pregnancy increased by 310% in France, 430% in England and Wales, and 696% in the United States. Various causes explain this inflation of multiple pregnancy. In England and Wales, in the United States, in Sweden, one quarter of this increase is attributable to an older maternal age at conception. It has been suggested that preconception intake of folic acid could raise the rate of twin pregnancy by 40%. In fact the prominent factor responsible for the high number of multiple pregnancies is the recent advances in the treatment of infertility. The multiple pregnancy rate is 6-8% after induction of ovulation with clomiphene citrate, and can be as high as 20-30% with gonadotropins. Assisted reproductive technologies (ART), represent the major provider of multiple pregnancy. Multiple births occur in 20% of pregnancies obtained by intra uterine insemination, and in 26% of pregnancies obtained by *in vitro* fertilization (IVF), or intracytoplasmic sperm injection (ICSI). In medically developed countries 30-50% of twin deliveries and 75% of triplet pregnancies occur after infertility treatments. In the United States 81% of multiple pregnancies originate from ART, 43% from IVF and 38% from

induction of ovulation alone. Therefore, if multiple pregnancy happened to be detrimental either to the health of the mother or to the wellbeing of the offspring, their excess rate should firmly incite to better master the management of infertility treatments. Indeed, multiple pregnancies are hazardous to both mothers and babies.

### **Maternal complications of multiple pregnancy**

Multiple pregnancy triple the risk of maternal death. In Europe the rate of maternal death is 5.2 per 100.000 births in singleton pregnancy, 14.9 per 100.000 births in multiple pregnancy. In developing countries the rate of maternal death ranges between 0.5 and 1% for singleton pregnancy, it reaches 2% for twin pregnancy and 6.3% for triplet pregnancy, with a relative risk of maternal death of 6.93 for multiple pregnancy compared to singletons (2). The cause of maternal complications with multiple pregnancy are listed in 1. The proportion of caesarean delivery is 30-50% for multiple birth, knowing that the risk of maternal death is fourfold after a caesarean section compared to a vaginal birth. The relative risk of post partum haemorrhage is 3-4.5 after multiple birth, including 4% coagulation disorders and 1.8% emergency hysterectomy. In addition, 12% of twin deliveries and 21% of triplet births need blood transfusions. The overall risk of transfer of the mother to an adult intensive care unit shifts from 0.3% with a singleton pregnancy to 3.1% after a twin delivery.

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\* Corresponding Address: Hôpital Saint Antoine, 184 rue du Faubourg Saint Antoine, 75012, Paris, France  
Email: j.milliez@sat.aphp.fr



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### ***Neonatal complications of multiple pregnancy***

Multiple pregnancies are hazardous for the neonates. They increase the risk of both premature delivery and low birth weight. Whereas only 4.6% of singleton pregnancies deliver before 37 weeks, 43.7% of twins are born before 37 weeks. The relative risk of premature birth for twins is 9. Similarly the relative risk of foetal growth retardation for twins is 11 compared to singletons, 52.7% of twins weighing less than 2500 gr at birth versus only 4.8% of singletons. In Canada, 39% of triplets are born before 33 weeks and 34% among triplets weigh less than 1500 gr at birth. Compared to singletons, triplets have a relative risk of 36 of being born before 33 weeks and a relative risk of 37 to have a birth weight below 1500gr. In England and Wales, in the mid nineties, perinatal mortality, stillbirth and early neonatal mortality during the first year of life, was 3.4 per thousand live births for singletons, sevenfold, 23.9 per thousand live births, for twins and fifteen fold, 50.6 per thousand live births, for triplets. Beyond perinatal events, the future neurodevelopment of offspring of multiple pregnancy is also of great concern. In the United Kingdom, the risk of cerebral palsy developing during childhood is 5.5 fold for twins and 19.5 fold for triplets compared to singletons. These figures are respectively 4.6 and 17.5 in Australia. In addition, not taking into account conjoined twins, the relative risk of congenital malformation for twins compared to singletons is 1.25.

Artificial reproductive technology may add further concerns for the outcome of pregnancy. The adverse perinatal events for children born after in vitro fertilization are essentially due to the high rate of multiple delivery (3). In vitro fertilization increases the risk of multiple pregnancy anytime more than two embryos are transferred into the uterus (4). Children born after in-vitro fertilization have a 3.7 risk of developing cerebral palsy compared to singletons, mostly because of premature birth and low birth weight linked to multiple pregnancy (5). Therefore it is strongly recommended that only one single embryo, at most two embryos, be transferred during IVF in order to limit the risk of neurological sequelae in the offspring. Finally, pregnancy obtained after intra cytoplasmic sperm injection or *in vitro* fertilization, entail a rate of 38% and 37% respectively of multiple pregnancy and carry a risk of major birth defects which is twice as high as for naturally conceived infants (6).

Besides detrimental effects on individual perinatal outcomes, multiple pregnancies have a broad impact on public health, the distribution of health

care resources and therefore on the whole community at large. Indeed overall, in Canada, multiple pregnancy account for 15.2% of total prematurity and 7.8% of cerebral palsy. In the United States, 11.2% of neonatal mortality and 3.4% of post neonatal mortality are attributable to multiple pregnancy. So, any effort to reduce the number of multiple pregnancies will contribute to improve the overall rate of neonatal mortality and morbidity.

Conversely any progress in the prevention and treatment of prematurity may be hindered by a parallel iatrogenic increase in multiple birth. Considering the hazards of multiple pregnancy for both pregnant women and their offspring, and taking into account the wide proportion of avoidable multiple pregnancy consecutive to infertility treatments, either induction of ovulation alone or ART, many countries, in particular Finland and Sweden, have formulated recommendations in order to avoid iatrogenic multiple pregnancy. They impose an improved management and mastering of ovulation induction and advocate a limitation, up to a maximum of two, in the number of embryos transferred after in vitro fertilization. The European Society of Human Reproduction, ESHRE, even recommends the transfer of one single embryo after ART. Despite repeated warnings on the hazards of multiple birth, in 1998, three or more embryos were still transferred after 44% of IVF or ICSI in the United Kingdom, after 48% of ART in France compared to only 9% in Finland and 4% in Sweden. In the United States, reimbursement of ART by health insurance companies, since it reduces the query to lower patient's own expenses and the compulsion for immediate results, allows to better limit the number of embryos transferred and dramatically reduces the risk of multiple pregnancy. For Reproductive Health Centres, the search of a maximum pregnancy rate as an index of best performance of infertility treatment and the quest of best financial incentives, are therefore ethically not acceptable. It is always offset by the dread of unpredictable health hazards for pregnant women and for their offspring, due to an uncontrolled rate of multiple pregnancy. Therefore the query of a maximum pregnancy rate to the detriment of the safety of mothers and offspring, because of an increased proportion of iatrogenic multiple pregnancy, should be held as unethical.

### ***Family impact of multiple pregnancy***

The impact of multiple births extends far beyond pregnancy and delivery. The intrusion within the

family of an unexpected number of newborns may disrupt the couple's psychological stability and induce unanticipated marital conflicts. Totally absorbed by the constant care required by twin or triplet neonates, the mother may unwillingly neglect her conjugal relationship or reduce the time shared with older siblings. The excitement and curiosity raised at first by a multiple birth among relatives, compassionate supporters or institutional care providers, usually fade rapidly, leaving alone parents who have to face unassisted the hardship of multiple child breeding. Physical and mental exhaustion may pervert the expected gratification of parenthood and induce for the parents, frustrated by their resented inability to achieve their parental duty, unjustified feelings of damaged self esteem or culpability. In addition financial expenses linked to the simultaneous care, raising and education of several children may impose an unbearable economic strain on a family with limited resources. It appears therefore mandatory to fully inform parents, beyond the immediate satisfaction and sense of happiness, of the long lasting consequences of multiple birth, in particular for iatrogenic multiple pregnancy induced by infertility treatments.

#### ***Multiple pregnancy and embryo-reduction***

Multiple pregnancy, either iatrogenic or occurring after a natural conception, entail a probability of serious risks which may not be acceptable to all couples. Parents may choose not to assume the hazards of multiple birth when they are made aware that the ongoing pregnancy involves more than one embryo. The reasons invoked for refusing the burden of multiple pregnancy are either the genuine health consequences for the babies and eventually for the mother, or the lack of psychological, social, financial resources to cater for a sudden unbearable challenge. Couples may be legitimately convinced that a better mastering of reproductive technology should render iatrogenic pregnancy avoidable and they demand, in the name of their autonomy, to choose the number of children they elect to raise. Similarly, parents of naturally conceived multiple embryos claim their right not to pursue the pregnancy if the number of embryos is too high for their expectations and they may apply for a voluntary abortion.

Since 1986 embryo-reduction is offered as an alternative to the ill effects of multiple pregnancy and its principle raised serious ethical debates (7). The technique is as effective through the abdominal or the trans-cervical route. For triplets

and pregnancies of greater order of magnitude, the medical advantages of embryo-reduction are sound. The natural abortion rate before twenty weeks of gestation for triplets is 20%, the rate of abortion induced by embryo reduction to either twins or singletons, is 8-9%, significantly lower (7). Although no specific data are available concerning the neurodevelopment of babies born after embryo-reduced pregnancies and the early selective abortion of their siblings, considering the later term at delivery and the greater birth weight for singletons and twins compared to triplets, it is very likely that the long range outcome of these embryo-reduced pregnancies is significantly improved. The technical justification for embryo-reduction is even more relevant for quadruplets and for an even higher number of embryos, since the perspective of such pregnancies is absolutely appalling. Some couples with a ongoing multiple pregnancy are conscious of the stakes and therefore request an unopposed access to embryo-reduction. Others on the contrary are far less favourable when this option is offered. For many couples, the need or the advantage of an embryo-reduction is not easy to understand after they have long yearned for childbearing and strived over multiple obstacles and minefields to achieve at last their first pregnancy. They are naturally reluctant to jeopardise the fate of a painstaking conception and to envisage the possibility of an eventual global miscarriage. The decision and the procedure itself, are emotionally stressful and their perspective immediately annihilates the euphoria of the newly gained expected motherhood. Per se, the crucifying end of life decision for one or more perfectly healthy embryos may be ethically criticized and appears as unjustified. Selective embryo-reduction for multiple pregnancy can be held by the parents as a medically added source of maternal distress, not as its remedy, as it could be for a voluntary abortion, and they nurture the hope the adverse consequences of multiple pregnancy may not be inelucable. Indeed the choice is ethically excruciating whenever the parents of multiple embryos are not adamantly decided to request an embryo-reduction. The pros and cons must be thoroughly exposed to them in any case, and formulated in such manner that the parents can make an autonomous decision and give a fully in normed consent. Nevertheless they should be suggestively advised that between two potential adverse hazards, the less ill event, embryo-reduction, is preferable. Again, the dilemma is practically absent for quadruplets since no one would deny the unacceptable risk of har-

bouring so many embryos. The well known image used to explain the dilemma is that of a life boat. When too many shipwrecked persons pretend to get aboard, irremediably it will sink. It is preferable to rescue a limited number of individuals rather than to loose all of them. The great ethical difficulty is to choose who is selected to survive and who has been designated to be sacrificed. For embryo-reduction it is usually decided at random, save the case where one embryo or two embryos would morphologically appear at echography to be most likely compromised.

The next question after the decision of embryo-reduction has been arrested, is the number of embryos to be sacrificed and conversely the number of embryos to preserve. A wide consensus exists such as an embryo-reduction of triplets or quadruplets to a twin pregnancy is the best compromise. The ethical objection which is often opposed to such a reduction (7) is that, through this strategy, pregnancy is assimilated to a casual matter of consumerism, where the quantity is taken in better account than the quality. In fact this argument is not appropriate for selective reduction from four or three embryos to two embryos. It becomes relevant when the project is to keep only one embryo, when the parents of triplets or quadruplets will not accept any pregnancy save a singleton pregnancy. It is even more striking when parents require the reduction of a iatrogenic twin pregnancy to a single embryo. The ethical dilemma is at its acme when the twin pregnancy occurs after a natural conception. Medically, the increased health risk for twin babies is indeed significant compared to singletons, but the extent of the added risk does not justify an embryoreduction, save rare and specific medical situations where a maternal ill condition would eventually alert against the extra burden of a twin pregnancy. In all other situations the choice to reduce a twin pregnancy to a singleton pregnancy is made on the grounds of personal convenience and preference, most often due to psychosocial considerations. No physician has an obligation to perform such an embryo-reduction if his/her personal conviction reproves the relevance of its motivation. Nevertheless, any physician who refuses to perform the procedure has the reverse obligation to address the couple to another practitioner who is likely to comply to the couples request. In fact beyond the personal beliefs of each individual physician, the ethical debate is often presented as a blackmail: if the selective embryo reduction is refused, firmly decided not to raise twins, the couple will opt for a voluntary global abortion. As for two sur-

vivors in the desert with a single ration of water, the compelling question therefore arises: should one be saved or should both die? Ethically, for "consequentialist" reasons, the less evil decision, one should live, provided the surviving neonate shall never be told the price of his mercy. The same precaution should apply for twin survivors after an embryoreduction for a triplet or a quadruplet pregnancy. In any case the availability of embryo-reduction should not be considered as an alibi, nor held as a convenient correction of the untoward side effects of ART procedures. It should not loosen the tight recommended control of infertility treatments and the necessity to avoid by all available means the occurrence of unwanted iatrogenic multiple pregnancy.

### ***FIGO ethical guidelines on iatrogenic multiple pregnancy (8).***

#### **Introduction**

1. In recent years there has been a dramatic increase in multiple pregnancies throughout the world. For example, some countries reported a doubling of twin pregnancies and the quadrupling of triplets over the last twenty years. The relative increase in higher order pregnancy has been even greater.
2. Undoubtedly, the main factor has been the use of ovulation inducing drugs and of multiple embryo transfer in the treatment of infertility. The increase in twin pregnancies may also be attributed in part to trends towards increased maternal age at conception.
3. The need for infertility treatment has also been rising sharply due to factors which include the impact of sexually transmitted diseases and the trend towards pregnancy at later age.
4. Multiple pregnancy has very serious implications for the mother and her offspring, for the family and the community, and for health service resources particularly where neonatal care services are limited or lacking

#### ***Recommendations***

1. Every effort should be made to prevent infertility through further research. Timely education and information about the risks and prevention of infertility are necessary. In addition, research and education are urgently required to improve the outcome of technologies of assisted reproduction.
2. The clinicians should take professional responsibility for optimising their own practices in the interests of avoiding multiple births.
3. Obstetrician-gynaecologists have an important

responsibility to make both the public as well as their patients aware of the many hazards associated with multiple pregnancy, especially with triplets and higher order pregnancies. In addition, they must make them aware that the high risk nature of multiple pregnancies requires an expertise that may not be available in some rural or smaller town areas.

4. Couples seeking treatment for infertility must be fully informed in writing of the numerous, complex and potentially far reaching risks of multiple pregnancy both to the woman and to their potential progeny. Counselling should also be available from experienced members of perinatal teams.

5. The misuse of drugs for the induction of ovulation is responsible for a great deal of iatrogenic multiple pregnancies. Therefore, those using these drugs should be familiar with the indications for their use, their adverse side effects and the methods of monitoring and preventing iatrogenic multiple pregnancy.

6. Obstetricians-gynaecologists using assisted reproductive technologies whether by the induction of ovulation or the transfer of embryos should aim to achieve singleton pregnancy. Under optimal conditions, single embryo transfer should be performed and good cryopreservation programme should be available. International and national professional bodies have a responsibility to issue recommendations for good practice with a view to reducing the incidence of iatrogenic multiple pregnancy. Centres should be certified or accredited in order to ensure a uniformly high standard.

7. In order to monitor and regulate professional practice, audit of the use of these technologies should include not only the fertility success rate but also statistics on singleton live births as well as the incidence of multiple pregnancy, the maternal and perinatal mortality and morbidity, the incidence of preterm delivery, and low birth weight, the occurrence of long term disabilities among offspring and the use of foetal reduction.

Couples should have access to reliable and standardized local centre statistics as well as national and international statistics.

8. The risks for both mother and the resulting children from triplet higher order pregnancies must be disclosed to and discussed with the couple. This discussion should include information about the availability, use and implications of foetal reduction.

9. Clinics and clinicians when discussing their results in public must avoid describing multiple

pregnancies as a success rather than a complication of treatment. The media should be aware that best professional opinion is to regard multiple pregnancies as a complication.

*Table 1: Frequency (%) of maternal complications in multiple pregnancy*

|                                    | Multiple Pregnancy | Singleton Pregnancy |
|------------------------------------|--------------------|---------------------|
| Threatened premature labour        | 76-86%             | 5%                  |
| Pre-eclampsia                      | 27-34%             | 2-3%                |
| Severe pre-eclampsia               | 24%                | 0.2-0.3%            |
| eclampsia                          | 2%                 | 0.1%                |
| HELLP syndrome                     | 9-10.5%            | 0.2%                |
| Abruptio placenta                  | 3.5%               | 0.3-0.6%            |
| Cardiomyopathy                     | 1.8%               | 0.2%                |
| Pulmonary thrombosis               | 1.8%               | 0.1-0.5%            |
| Pulmonary oedema                   | 3.5%               | 0.2%                |
| Severe anemia                      | 27-58%             | 10%                 |
| Acute fatty liver                  | 1.8-7%             | 1/10,000            |
| Gestational diabetes               | 7-10.5%            | 5%                  |
| Placenta previa                    | 1%                 | 0.25%               |
| Premature rupture of the membranes | 17; 5-20%          | 10%                 |

*Table 2: Simplified way of counselling parents about outcome of extremely premature babies (T.Koh Lancet 1996; 348-963)*

| Gestation (weeks) | Survival % | Survival without handicap% |
|-------------------|------------|----------------------------|
| 24                | 40         | 40                         |
| 25                | 50         | 50                         |
| 26                | 60         | 60                         |
| 27                | 70         | 70                         |
| 28                | 80         | 80                         |
| 29                | 90         | 90                         |

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