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COMMENTARY

Reducing multiple pregnancies after assisted reproduction treatment: Québec says ‘Yes, we can!’

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Abstract Multiple pregnancy (MP) is widely recognized as the single biggest risk to children born as a result of assisted reproduction treatment. There is an emerging trend in Europe and Canada to promote single-embryo transfer (SET). In this issue, Gleicher argues that twin pregnancies should not be seen as an unfavourable outcome of assisted reproduction treatment. He argues that SET policies ‘make no sense’ since they will aggravate already unsatisfactory population growth in some countries. He also argues that governmental intervention to impose SET policies, despite proving successful in reducing MP, are inappropriate. The overwhelming evidence in the literature indicates that his opinion is not supported by credible data. Views should be based on solid data rather than personal judgement. Governmental interventions to reduce twin pregnancies, as demonstrated previously in Belgium and now in Québec, have been successful. The risks of twin pregnancies are real and borne by women and children, not their doctors. Doctors managing infertile couples are no longer entitled to take risks with the health of the next generation. 

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‘The extent to which beliefs are based on evidence is very much less than believers suppose’ (Bertrand Russell, 1928)

Gleicher (2011) argues that twin pregnancies should not be seen as an unfavourable outcome of assisted reproduction treatment; they present an opportunity to provide the preferred outcome of many infertile couples – to have two children from one treatment cycle – and are less expensive and risky than two singleton pregnancies. He is particularly critical of the emerging trend in Europe and Canada to promote single-embryo transfer (SET), believing such initiatives are unwarranted and counterproductive, as they will lead to the birth of fewer children. Bizarrely he argues that SET policies ‘make no sense’ since they will aggravate already unsatisfactory population growth in some

countries. While free to rail against the consensus (HFEA, 2011), is his ‘opinion piece’ supported by convincing data?

Should twin pregnancy not be considered a complication?

Those who work in obstetric and neonatal units are acutely aware of the well-documented maternal and fetal complications associated with twin pregnancy and of assisted reproduction treatment’s contribution to the numbers. Children born in multiple pregnancies are at risk of prematurity and low birthweight (<2500 g), which are the main causes of increased immediate mortality and morbidity, long-term disabilities including cerebral palsy and limitation in motor

and cognitive skills. The neonatal death rate of singleton pregnancies is 7.8 per 1000 live births; this number increases seven-fold in twins (Oleszczuk et al., 2003). Similarly, the infant mortality rate of singleton pregnancies is 11.2 per 1000 live births and increases six-fold in twins (Oleszczuk et al., 2003). The most recently published Centers for Disease Control report of outcomes of assisted reproduction treatment (<http://www.cdc.gov/art/>) in the USA indicates that among assisted reproduction births, 61% of twins and 96% of triplets were born preterm compared with single-fetus pregnancies (12%), and that 55.5% of assisted reproduction treatment twins and 92% of triplets were of low birthweight. Even when a multiple-fetus assisted reproduction pregnancy results in a singleton delivery, the risk of prematurity is also raised (19% versus 12%), and the percentage of low birthweight infants is higher for those from multiple-fetus pregnancies (about 15%) than those from single-fetus pregnancies (9%). These facts demonstrate that simply being an assisted reproduction twin, or starting out as an assisted reproduction twin even when a singleton results, increases neonatal risk. Double-embryo transfer (DET) does not limit the risk to twins; 1.2% of young women who had DET had a triplet live birth, which does not include those children lost prior to viability. Unsurprisingly, multiple pregnancy is widely recognized as the single biggest risk to children born as a result of assisted reproduction treatment (http://www.hfea.gov.uk/docs/MBSET_report.pdf).

In addition, the Board of Health Sciences Policy has estimated the mean cost of each preterm infant to be US\$ 51,600 (Board on Health Sciences Policy, 2006). The financial burden of these assisted reproduction-associated preterm deliveries is estimated to be approximately US\$ 1 billion annually which approaches the cost of assisted reproduction treatment itself (Bromera et al., 2011). Given the above statistics, we question the wisdom of encouraging more twin pregnancies as it appears to be neither safe nor cost-effective.

Are the complications of twin pregnancies equivalent or less than the sum of complications associated with two singleton pregnancies?

The central argument of those who reject the consensus view is that twin pregnancy presents an opportunity to produce two children in a single live-birth event and as such avoid the risks and costs of trying for another pregnancy. They assert that the complications associated with twin pregnancy and childbirth are equivalent to the sum of complications of two singleton pregnancies, and that it is more cost effective to aim for twin rather than singleton pregnancies. The data above demonstrate clearly that with twin pregnancies, two babies are exposed to an exponentially higher risk of prematurity, low birthweight and neonatal and infant mortality since both children are exposed to the enhanced risk at once, rather than the smaller risk in two separate live-birth events. Moreover, many risks are summative, such as low birthweight and prematurity, and the enhanced medical and obstetric risks to the mother of carrying and giving birth to twins.

Do most infertile patients really view twin pregnancies as a desired outcome?

Unfortunately, most studies addressing this issue have methodological flaws. The assertion that the majority of patients undergoing fertility treatment would prefer twins paid little attention to the context, including the type or the timing of the question, and the population surveyed. There is little consistency among the studies in the kind of information presented to the surveyed patients about the risks of twin pregnancies before asking them this question and the validity of hypothetical answers to a hypothetical question is uncertain. Indeed, recent work shows that patients' preferences for a singleton or twins are not stable during IVF treatment (Fidellers et al., 2011). However, two large studies in the USA (Ryan et al., 2004) and Canada (Child et al., 2004) which asked the right question at the right time, i.e. before embarking on fertility treatment, found a minority of patients (20.3% and 38.9%, respectively) expressed this desire. This is at odds with Gleicher's old (1995) study in an infertile population at treatment or within 1 year of treatment that reported a much higher rate (67%) but with a very poor (16%) response rate. It has also been reported that a high proportion of patients had no preference for either a singleton or twins (Twisk et al., 2007), and a desire for DET might reflect patients maximizing their chances of conceiving a singleton (Newton et al., 2007). Additionally, preference for twins may be the direct result of the availability of DET. Doctor-led behaviour should not be discounted; it has been suggested that patients may accept what is offered (Garel et al., 2008) and that their views will be substantially influenced by the kind of information presented to them, which often will reflect clinician prejudice.

The right to self-determination: should clinicians remain passive when their patients make a risky choice?

The difficulty here is in presenting a realistic picture of risk, which may be within the experience of the clinician and the obstetric team, but wholly theoretical in the mind of the patient. Assisted reproduction patients' decision making is influenced by many factors. Among these are duration of infertility, funding source, prognosis of their treatment and their own previous experience. The promise of a higher and more rapid chance of pregnancy with DET is difficult to weigh against a theoretical risk of twins and small chance of damage. Some patients have expressed a preference for a handicapped child rather than no pregnancy at all from their treatment (Scotland et al., 2007). The clinician should provide the information, at least for the young woman in her first cycle, that the chances of pregnancy whether with her fresh or subsequent frozen cycle are so good that the risk is needless and not worth taking (Thurin et al., 2004). Even with SET restricted to this group alone, significant impact can be made on multiple pregnancy rates (Khalaf et al., 2008). Clinical leadership is a major problem especially in a commercially competitive environment, where clinicians may be distracted by success rates and miss more important long-term health outcomes (Templeton, 2010). Even in pursuit of the right to self-determination, it is unlikely Gleicher

would be persuaded that a three-embryo transfer in a young woman in her first cycle with a very high chance of producing a pregnancy would be in her best interests. We submit that if assisted reproduction clinics themselves had to bear the neonatal costs for the premature twin deliveries created, DET would largely disappear.

In the face of ambivalent clinical leadership, is government intervention appropriate?

Many countries introduced strict regulations with respect to assisted reproduction treatment, limiting the maximum number of embryos transferred and encouraging a reduction in multiple-embryo transfers, in recognition of the complications and cost associated with multiple pregnancies, especially triplets. In 2002, in the absence of clinical leadership, the Human Fertilisation and Embryology Authority introduced a limit of two embryos for those under 40 years, which reduced the triplet pregnancy rate almost to pre-IVF levels (HFEA, 2006). Reducing high multiples is relatively easy as all one has to do, for instance, is to transfer one embryo less each transfer. Reducing twin pregnancies is the difficult part as this can only be effectively achieved by SET. Even the American Society for Reproductive Medicine guidelines (The Practice Committee of the ASRM and the Practice Committee of the Society for Assisted Reproductive Technology, 2009) have significantly diminished triplet rates in the USA, but at a cost of increasing twin rates. The same is true for the UK. Voluntary or semi-voluntary programmes aimed at reduction of multiple pregnancies do not work well – both the UK (Templeton, 2010) and the USA (Bromera et al., 2011) fall in those categories. The smartest government intervention is probably that implemented by the Belgian government in 2003, which nearly eradicated triplet pregnancies and brought twin pregnancies down significantly to about 12% of assisted

reproduction pregnancies (Figure 1). It clearly shows that triplet pregnancies are now nearly non-existent and that twin pregnancies are significantly reduced as well compared with the period before 2003 when the embryo transfer rules became mandatory.

A ‘carrot and stick’ approach may be effective for both patient and provider. Experience from Europe indicates that when government has intervened by increasing the level of funding coupled with employing a SET policy in the appropriate patients, significant reduction in multiple pregnancies has been achieved. Whereas generally there can be little scope for a wholesale move to SET for everyone, there are groups in whom SET is highly effective and safe. The Québec experience (Bissonnette et al., 2011) should be credited with achieving a remarkable reduction in multiple pregnancies within a relatively short period of time and through resorting to elective SET (eSET) in only 50% of their patients. It is important to emphasize that the term eSET remains valid on two counts: (i) technically speaking, transferring a single embryo when more are available can only be described as elective; (ii) the policy made allowance for transferring more than one embryo under suboptimal circumstances; therefore, it was not a blanket policy, and in practice, only 50% received eSET.

The assertion by Dr Gleicher that the province of Québec will be losing 33% of IVF newborns (and their lifelong earning power) annually is fundamentally flawed because: (i) not all clinical pregnancies would lead to a live birth; (ii) the number of pregnancies resulting from the use of frozen embryos is not known, which is bound to be higher after the initiative (as more embryos are likely to have been frozen); and (iii) the focus is on mere numbers of children rather than on numbers of healthy children (more likely with singleton pregnancies than with twins).

Furthermore, the omission of the potential harm to which a significant proportion of these multiple pregnancies and the resulting children would have been exposed are at

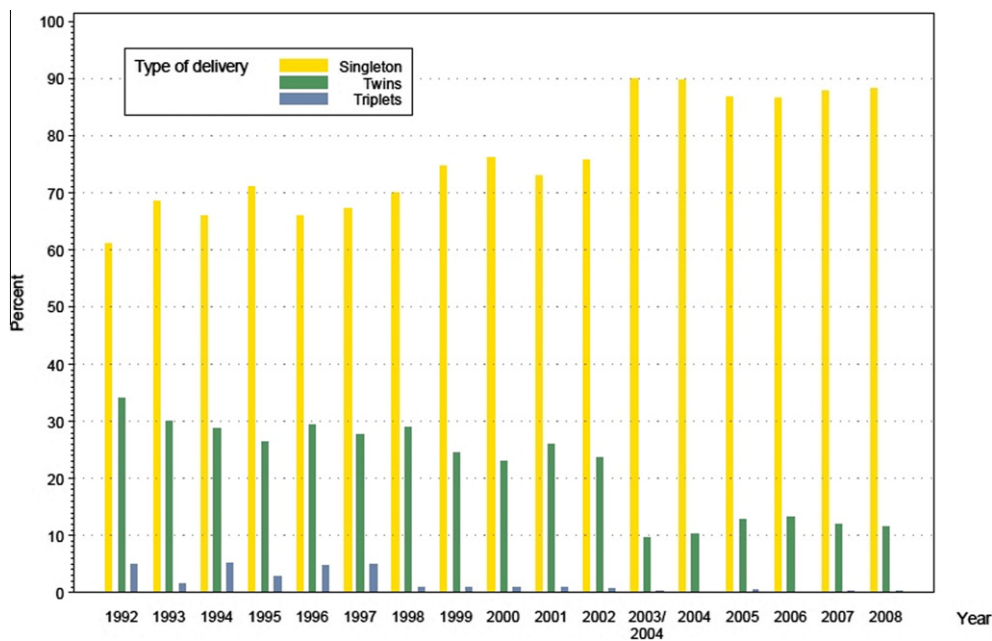


Figure 1 Own fresh cycles: changes in number of single and multiple deliveries with time (reproduced with permission from Belgian College of Physicians for Reproductive Medicine (2008)).

odds with the professional obligation to give precedence to avoiding harm.

Gleicher sees the success of the Québec initiative through a tainted lens which focuses on the potential loss of a number of children through the substantial reduction of twins whilst completely ignoring the number of children spared from being lost or damaged due to complications of miscarriage or prematurity. A fairer description of the initiative would be that despite the loss of 11% of pregnancies, it achieved a reduction by 86% of the Multiple Pregnancy Rate (MPR) and the associated complications, whilst still maintaining the possibilities of pregnancy for many in the frozen cycle that could follow.

This view is supported using data from the Royal Victoria Hospital records and the Canadian Assisted Reproduction Technologies Register's 2005 report, where researchers calculated that a pan-Canadian SET policy would prevent 30–40 deaths, about 35 severe intracranial haemorrhages and about 16 retinal surgeries (<http://tinyurl.com/3n5mg94>). The study concluded that a mandatory SET policy would be of substantial benefit to the health of Canadian babies while still benefiting infertile couples.

Conclusions

Views should be based on solid data rather than personal judgement. The compelling statistics above show that the risks of twin pregnancies are real and borne by women and children, not their doctors. We agree with Templeton (2010) that 'Doctors managing infertile couples are no longer entitled to take risks with the health of the next generation'. The sceptical and ambivalent attitude of a minority of clinicians is unsubstantiated by credible data and is no longer acceptable in the face of better understanding for whom SET is appropriate, and with improving cryopreservation success. Government intervention may be necessary to curtail excessive levels of multiple births, particularly when they bear the costs of adverse outcomes, provided that universal SET is not mandated. Where IVF is state funded, provision of appropriate support including cryopreservation transfer cycles, will drive SET as a self-determined choice given the data about multiple-pregnancy risk. SET provides couples with more chances of achieving a pregnancy and improves the likelihood of having healthy term children. The Québec initiative is a good example of these interventions and should be encouraged rather than disparaged. Researchers are advised to report their cumulative pregnancies and live-term births per stimulation cycle to dispel the misapprehension that this development would result in delivery of fewer children.

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