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COMMENTARY

Eliminating multiple pregnancies: an appropriate target for government intervention?

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Abstract The manuscript in this issue of the journal by Bissonette et al. reports on a new government-sponsored intervention into the practice of IVF within the province of Quebec, Canada, which in the authors' opinion highly successfully reduced twinning rates, while maintaining overall acceptable pregnancy rates. Given the opportunity to comment, their manuscript, in my opinion, only reemphasizes why, despite wide professional support, the concept of single embryo transfer (SET) is: (i) damaging to most infertility patients by reducing pregnancy chances; (ii) does so without compensatory benefits; (iii) impinges on patients' rights to self-determination; (iv) has significant negative impact on IVF-generated birth rates; and (v) thus, demonstrating, once more, that governments should not interfere with the patient–physician relationships. 

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When Bissonette et al. (2011) initially submitted their manuscript included in this issue, I excused myself as section editor from administrating the review process because I (and my colleague David H. Barad) hold opposing opinions on the utility of single-embryo transfer (SET) (Gleicher and Barad, 2008a–c, 2009). I was then asked by the Senior Editors to express an opinion, when asked to contribute this commentary on the paper, which reports the apparently quite remarkable story of a government-intervention that succeeded in controlling multiple-pregnancy rates in association with IVF (Bissonette et al., 2011).

In August 2010, the provincial government of Québec, Canada, started funding assisted reproduction treatment through the province's health programme. In parallel, legislation was introduced 'to control' assisted reproduction treatment, as it would be practised in the province. Those controls included strict restrictions on number of embryos to be transferred per cycle.

The authors note that the aim was SET in every possible cycle (see later why the term 'elective single-embryo transfer' is avoided in this commentary). Transfer of more than one embryo required physician justification, specifically describing the 'suboptimal' conditions, allowing for deviations.

In the first 3 months of the programme, five assisted reproduction centres in the province performed 1353 IVF cycles under these government regulations, 50% with SET, an overall pregnancy rate of 32% and a multiple-pregnancy rate of 3.7%. This, according to the authors, compared very favourably to the preceding year, when only 1.6% of cycles had SET, the clinical pregnancy rate had been 42.8% and the multiple-pregnancy rate was 25.6%. They further concluded that the programme created an environment that favoured rapid implementation of SET, rapid declines in multiple pregnancies, while maintaining acceptable pregnancy rates.

In reaching these conclusions, Bissonette and associates reflect a quickly spreading mindset within the profession,

unified in considering twin pregnancies as an adverse treatment outcome of IVF and aggressively promoting SET (Schieve, 2006), if necessary, even via government interventions (Saldeen and Sunderström, 2005). I have strongly disagreed with both of these contentions (Gleicher and Barad, 2008a–b, 2009) and actually consider the paper of Bissonnette and associates as further evidence in support of my position.

The alleged rationale for SET

Since the literature is practically unanimous that double-embryo transfer (DET) offers significantly higher pregnancy chances than SET (McLernon et al., 2010), there remain only two arguments in favour of SET: alleged reduction of maternal and fetal risks and medical costs. These apparent benefits stem from widely accepted increased risks and medical costs of twin deliveries in comparison to singletons for mothers (Mackay et al., 2006) and offspring (Ombelet et al., 2006). As SET significantly reduces twin pregnancies in comparison to DET (McLernon et al., 2010), under this mindset, SET, in parallel, reduces risks and costs to mothers and offspring alike (McLernon et al., 2010; Schieve, 2006).

As no other benefits support SET over DET, and DET offers superior pregnancy chances (McLernon et al., 2010), one therefore has to conclude that, should this widely accepted evidence of twin pregnancies being more risky and costly be refuted, no reason to favour SET over DET would be left in patients desirous of twins.

That risks and costs of twin pregnancies do not significantly exceed those of singleton gestations was, indeed, quite unequivocally demonstrated (Gleicher and Barad, 2009). This, on first glance, may appear incredulous, even impossible! As noted above, obstetric/perinatal data in the literature, of course, beyond reasonable doubt, demonstrate increased prematurity (and other complications) in twin pregnancies in comparison to singletons, even with best perinatal management (Ombelet et al., 2006). Yet, what if data analysis and conclusions of all studies making such a point, in regards to an infertility treatment paradigm, can be proved wrong?

The reason why this is indeed the case is rather simple and involves very fundamental concepts of study design and medical statistics: data generated within one study context are only applicable to that context and cannot be exported. For example, despite obvious benefits from mouse studies to the understanding of the human condition, mouse data cannot be automatically transferred to humans. Data from one patient population cannot be automatically transferred to another. While this most basic fact of study design and data analysis represents a cornerstone of scientific peer review in medicine, this kind of automatic transfer from one context to another is exactly what has been driving the argument in favour of SET since its inception.

Let me explain further. A great majority of infertile women enter treatment wishing for more than one child to complete their family (Gleicher and Barad, 2009). This, indeed, is a principal reason why so many are desirous of twins, first reported by me in 1995 (Gleicher et al., 1995)

and reconfirmed by many authors since (Gleicher and Barad, 2009). For a patient desirous of two children, the question arises how can she with lowest risks and costs be helped to two offspring? The options are obvious in such a prospective treatment paradigm: with a reference point of two newborns, she can have two children from either one twin pregnancy or two consecutive singleton gestations. The preferred option will be the one with lower risks and costs.

This prospective treatment paradigm for the infertility specialist stands in stark contrast to the traditional obstetric/perinatal treatment paradigm, which by definition is retrospective. Moreover, while the infertility paradigm has a reference point of the birth of two newborns (independent of how many treatment cycles and pregnancies it takes to achieve this goal), the retrospective obstetric/perinatal paradigm uses the reference point of always one pregnancy (independent of how many children are delivered in that pregnancy). Fertility treatment and obstetric/perinatal paradigms, therefore, have little in common and data from one are not automatically transferable to the other.

In analogy to mouse data not being applicable to the human experience and data from one patient population not being transferrable to another, data from the retrospective obstetric/perinatal paradigm is, therefore, not applicable to a prospective infertility treatment paradigm. The principal reason is obvious: the obstetric/perinatal paradigm compares one pregnancy, with one singleton outcome, to one twin birth involving two offspring, while a correct prospective infertility paradigm compares outcomes of one twin pregnancy to two independent consecutive singleton pregnancies.

Quite surprisingly, the peer review process has, however, routinely permitted colleagues to use data from retrospective obstetric/perinatal studies to support, within a prospective fertility treatment paradigm, arguments in favour of SET. Using limited available data, methodically correct comparisons within a prospective infertility treatment paradigm demonstrate, however, that twin pregnancies no longer significantly increase risks or costs in comparison to two consecutive singleton gestations. Indeed, in many outcome parameters, the opposite is the case (Gleicher and Barad, 2009; Lamazou et al., 2011).

This was not only demonstrated in my study of published data in the literature (Gleicher and Barad, 2009) but, more recently, also in a French study, which matched, at one institution and controlled for maternal age, outcomes between one twin pregnancy and two consecutive singleton gestations (Lamazou et al., 2011). Lamazou et al. (2011) from René Frydman's department in Clamart, concluded that 'two successive pregnancies are often an uncertain outcome after IVF, and also associated with [expected] complications of repeat procedures'. A twin pregnancy in their opinion 'could represent a reasonable option to accomplish parental desire of having two children' (quoted with permission from the authors, 10 February 2011).

Why government intervention?

Québec, like mostly Northern European countries before (<http://www.oneatatime.org.uk/372.htm>, accessed 12

February 2011), has legislatively restricted the number of embryos allowed to be transferred. As in all of these places, governments usually pay for assisted reproduction treatment, it is difficult to argue with their right to control costs. One, however, can question the wisdom of their decisions, and, therefore, how well governments are really suited to intervene into the medical decision-making process between patient and physician?

It is difficult to hold governments responsible for the wisdom of those decisions. They, most likely, are acting on the advice of medical colleagues or professional organizations. Indeed, colleagues, quite surprisingly, from very early on have suggested government interventions in enforcing SET (Saldeen and Sunderström, 2005). From a US point of view this is difficult to understand, but likely reflects varying philosophies on both sides of the Atlantic in regards to how health care should be administered. Following a more European-style model, our Canadian colleagues, Bissonnette et al. (2011), appear sympathetic to their local government's intervention. They, in my opinion, do so, like other proponents of SET, with the typical unintended consequences of most government programmes and to the disadvantage of their patients.

The patients' right to self-determination

Although the above-noted statistical argument alone, in my opinion, invalidates the worldwide drive towards SET, I am equally struck by how colleagues are willing to ignore their patients' rights to self-determination. Studies have repeatedly demonstrated that almost nothing is more important to infertility patients than (quick) pregnancy success (Scotland et al., 2007), and even amongst well-educated patients, a large majority consider twin pregnancies highly desirable outcomes (Gleicher and Barad, 2009; Gleicher et al., 1995). Yet, proponents of SET assume to know better! (McLernon et al., 2010; Schieve, 2006).

This is a principal reason why I do not use the terminology of elective single-embryo transfer, utilized by Bissonnette et al. Nothing under current SET practices appears to me, from a patient's point of view, as 'elective'. Indeed, I consider the imposition of SET, at the expense of pregnancy chances and without compensatory clinical or financial gains, coercive and incompatible with a patient's right towards self-determination.

Bissonnette et al. consider the 31.6% pregnancy rate per embryo transfer as acceptable. Yet, the pregnancy rate was 42.8% before Québec instituted the SET programme. The programme, thus, reduced the pregnancy chance of every patient in the province by a remarkable 26.2% of pregnancy chance or 11.2 points in pregnancy rate. Let me take this calculation even further: the programme also reduced the multiple-pregnancy rate from 25.6% to 3.7%, thus eliminating 21.9% of multiple deliveries. If, for simplicity sake, it is assumed that all of those multiples were twins, another 21.9% of IVF cycles lost a second delivered infant. Combining these two numbers, Québec lost in one single legislative swoop an amazing 33.1% of its IVF children. This may be mildly exaggerated since not all multiples are, of course, twins, but approximately a third of all IVF newborns may be 'missing' in Québec in the New Year.

The SET versus DET debate is not a replay of the debate 10 years ago on the transfer of three (or more) embryos versus DET. When Templeton and Morris in their groundbreaking paper demonstrated the benefits of DET, they did so by demonstrating not only that DET reduced multiples but also that DET did so without negatively impacting pregnancy chances, which is what really won the argument (Templeton and Morris, 1998). Even strong proponents of SET, of course, have to acknowledge the lower pregnancy rate with SET than DET (McLernon et al., 2010).

Attempts at spinning the issue, however, continue: while a recent meta-analysis convincingly demonstrated lower pregnancy rates with SET, the authors attempted to rescue the SET argument by claiming that 'additional frozen SETs almost completely overcome such shortcomings in fresh pregnancy rates' (McLernon et al., 2010). While 'almost,' of course, should never pass peer review, the argument is also categorically incorrect: failing to conceive in a fresh IVF cycle delays pregnancy and increases time to pregnancy and delivery. Most infertility patients consider this a very undesirable option (Scotland et al., 2007).

Lamazou et al. (2011) in addition, unequivocally demonstrated that such delays can, in addition, lead to unexpected consequences and affect a patient's pregnancy chances. This is, of course, highly relevant for infertility patients (Scotland et al., 2007). In addition, failure to conceive also means additional costs for additional frozen–thawed cycles. What is totally overlooked by proponents of SET is that, even once the patient has her first child, there are those who could have had two children through a twin pregnancy who are further financially challenged by requiring additional treatment at significant additional cost to match the number of children they otherwise would have delivered.

A final word about costs

Since government interventions are mostly cost-driven, there are a few more thoughts about costs. It, of course, is true that an obstetric/perinatal comparison of medical costs between one singleton and one twin pregnancy will demonstrate much higher costs for the twin pregnancy (Gleicher and Barad, 2009). But, even ignoring that such a comparison is statistically incorrect and that a comparison of one twin with two singleton pregnancies no longer demonstrates these cost disadvantages, correct cost studies cannot be time limited.

Correctly performed cost studies (one should be able to assume that governments are qualified to conduct those) cannot only consider healthcare costs generated by adverse obstetric outcomes in the first few weeks and months after delivery. They also have to consider the lifelong earning potentials of healthy born twins. Returning to the approximately 33% of IVF newborns (and their lifelong earning power) that the province of Québec will be losing annually until repeal of the programme, even the most sceptical observer will have to acknowledge that current government policies in favour of SET make no sense (Gleicher and Barad, 2009). Especially in countries where population growth is unsatisfactory (Canada and Europe), governments should actually encourage DET and twin deliveries (Gleicher and Barad, 2009; Hoorens et al., 2007).

Conclusions

On closer inspection, the Québec experience, therefore, does not look as good as presented by Bissonnette et al. (2011). Indeed, one can take this experience as a good example why medical care should always be based on a decision-making process between patient and physician and not on legislators (mostly lawyers, of course) and their interventions.

Here is one more reason to keep government out of medicine. Let us for a moment assume the impossible, that this commentary, overnight, convinces colleagues all over the world of their mistaken ways when it comes to SET. World-wide medical practice then could, and indeed most likely would, change very quickly. Imagine, however, how long the change would take in those countries where legislatures enshrined the practice of SET into their countries' laws.

Bissonnette and associates have offered me another opportunity to review how obviously wrong current SET practices are for the large majority of infertility patients desirous of twins. For this I should be grateful, even if I cannot agree with their conclusions.

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