

Commentary

Patients are entitled to maximal IVF pregnancy rates



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Abstract

IVF programmes generally follow treatment protocols that strive for best outcomes. Deviations from such established protocols, even if conceptionally well supported, always risk potentially adverse effects on pregnancy chances. Successful pregnancy represents, however, the principal motivation for all fertility treatments. As a universal medical principle, patients are, therefore, entitled to maximal professional efforts towards their desired outcomes in the safest, quickest and most cost-effective ways. For IVF this means, as multiple patient queries in the literature have demonstrated, the following parameters in this order of importance: highest possible pregnancy rates, lowest possible risks, shortest possible time and lowest possible cost. Some recently widely propagated changes to broadly utilized practice patterns in IVF now, *post factum*, have been determined to be clinically useless and, in addition, have been shown to adversely affect pregnancy chances. Also *post factum*, this has led to the acknowledgement that significant modifications to established IVF practice should be introduced with caution. In view of the quite satisfactory IVF pregnancy rates that are currently achieved, the uncontrolled introduction of significant protocol modifications, which may adversely affect IVF outcomes, should no longer be acceptable practice as such unproven practice modifications may violate the patient's entitlement to maximally achievable pregnancy rates.

Keywords: DET, embryo transfer, infertility, multiple births, preimplantation genetic screening, SET

Introduction

A recent communication by Ankum *et al.* (2008) discussed in great detail a relatively recently introduced new technology, which worldwide had been clinically implemented into IVF without prior evidence of effectiveness. While many believe this to represent an isolated incidence of communal professional misjudgement, by building upon these authors' conclusions, this communication points out that the uncontrolled introduction of new techniques into IVF has historically been a cornerstone in the very successful evolution of clinical IVF. It should not, therefore, be surprising that this pattern continues on a much broader scale than is often appreciated. The evolving maturity of IVF now, however, mandates a more disciplined approach since, for the first time in the history of IVF, uncontrolled technology modifications

run the risk of adversely affecting the continuous outcome improvements in pregnancies observed worldwide since IVF's inception.

Some historical background

While maybe somewhat different from Europe and other parts of the world, IVF's evolution has been unique within the USA. Without any support from the federal government and almost completely financed by clinical practice earnings (Gleicher, 2003), one, indeed, has to be, as Toner (2002) put it, 'proud of the progress that was made'.

Because developments were not funded via traditional research-granting mechanisms, progress was often made via uncontrolled, practical clinical trials (and errors). This may be best demonstrated through a subject that remains contentious to this day: the number of embryos that should be transferred.

With pregnancy rates still very low, often in single digits, vastly large numbers, by today's standards, of embryos were replaced. While embryo selection evolved, embryo culture conditions improved, embryo cryopreservation was developed and intracytoplasmic sperm injection (ICSI) revolutionized the treatment of male infertility (all, of course, introduced without proper clinical trials), implantation and pregnancy rates increased in parallel. Not surprisingly, an epidemic of high-order multiple births ensued (Jones Jr, 2003).

Recognizing the problem, the profession quickly developed remedies. Professional societies issued a series of progressively more restrictive embryo transfer guidelines (American Society for Reproductive Medicine, 2004). But, even more importantly, investigators initiated statistically well-controlled modifications to IVF practice patterns, with probably the most influential being the study of Templeton and Morris (1998) that demonstrated that double embryo transfers (DET), in comparison to larger embryo numbers, did not reduce pregnancy chances, but did significantly reduce high-order multiple birth rates. As a consequence, multiple births after IVF started again to decline (Toner, 2002).

Therefore, when Lambert (2002) criticized the evolution of IVF, which had led to excessive multiple births and suggested that, had the concept of multiple embryo transfer ever been submitted for approval to an institutional review board, it would never have passed muster, Gleicher (2003) strongly objected. The counterargument was that his proposed scenario, in the early days of IVF, would never have resulted in minimally acceptable pregnancy rates to the public and that IVF, therefore, probably would never have survived in the economic market place (Gleicher, 2003).

However, the definition of expected minimal clinical success has changed over time, as one would expect. As pregnancy rates progressively improved (Toner, 2002), public expectations grew in parallel. And, at least within the USA, healthy competition in the market place has continued to feed this development, leading to the highest pregnancy rates in the world, although also leading to above-average multiple pregnancy rates (Gleicher *et al.*, 2006, 2007).

This highly successful, mostly market-driven system now, however, faces new and unprecedented challenges that threaten further progress and indeed may reverse past successes.

Modifying IVF protocols

Even in the early trial-and-error phases of IVF, most programmes functioned under some form of supervision. In the USA, this usually meant annual reporting to institutional review boards. Changes in protocols, however, took place frequently and were only rarely subjected to prior institutional review board approval. What factors constituted significant enough changes in practice patterns, and thus deserving of experimental study

protocols and informed consents, varied between centres. Ideas diverged quite significantly from what most investigators nowadays would consider appropriate.

The reasons for such an approach were quite obvious: with pregnancy rates still very low, the potential risks of adversely affecting them were small. Considering how poor pregnancy rates were overall, changes could only lead to outcome improvements. Ethically therefore, it appeared appropriate to allow for a degree of 'experimentation', and rapidly improving IVF pregnancy rates supported such an approach.

Despite obvious differences between countries and even continents (Gleicher, *et al.*, 2006, 2007), IVF pregnancy rates today are at all-time highs everywhere. The risks of adversely affecting them by changing treatment protocols is much greater than before and the traditional trial-and-error approaches towards changes in practice patterns no longer seem ethically appropriate.

This argument is further strengthened by the fact that, at least in the USA and Europe where continent-wide outcome data sets are published annually, IVF patients now have guidance as to what to expect. Once realistic outcome expectations exist, patients quite obviously should be entitled to have them met. This, in turn, means that modifications to routine IVF protocols, with the potential of altering outcomes, should not be introduced unless they have been proven not to harm outcomes or are introduced under study conditions, and with appropriate informed consents. With the successes of maturity also come obligations. Expected pregnancy rates nowadays are too high to allow significant untested modifications to standard IVF protocols entering clinical practice without proper prior evaluations.

This seemingly so obvious fact appears, however, significantly less obvious when recent events in the profession are considered. Introduced with considerable fanfare, a number of major modifications to standard IVF practices have recently proven rather disappointing and, in addition, are very likely to adversely affect IVF outcomes. Amongst those, preimplantation genetic screening (PGS) represents probably the best example.

Proposed under the very credible hypothesis that transfers of only euploid embryos should improve pregnancy rates and decrease miscarriage rates with IVF, PGS failed to demonstrate such benefits when tested in a limited number of studies (Werlin *et al.*, 2003; Staessen *et al.*, 2004; Stevens *et al.*, 2004). A recently published paper reanalysed previously published data and concluded that PGS was 'not ready for prime time' for attempts to improve IVF outcomes and may indeed, reduce pregnancy chances in many women (Gleicher *et al.*, 2008). It would exceed the framework of this communication to present further detail here. The interested reader is referred for such detail to the previously cited publication. The possibility of potential risk to pregnancy rates was also confirmed by a prospectively randomized study of PGS, reported out of The Netherlands (Mastenbroek *et al.*, 2007).

Not surprisingly, the Practice Committees of the American Society for Reproductive Medicine and Society for Assisted Reproductive Technology recently concluded that available evidence does not support the use of PGS, as currently performed,

to improve live-birth rates in patients with advanced maternal age, previous implantation failure or recurrent pregnancy loss. Similar sentiments were also expressed by European authorities (Devroey and Fauser, 2007; Ankum *et al.*, 2008)

Another major example for the inadequate introduction of new concepts into IVF practice is represented by the now widely propagated concept of single embryo transfer (SET). Increasingly popular on both sides of the Atlantic, a critical evaluation of SET, as recently presented by us in a series of articles (Gleicher and Barad 2008a,b,c) also allows for the conclusion that SET represents a major change in IVF practice pattern, lacking of any obvious benefit to patients but reducing their chances of conceiving.

Initially attempting to mimic the correct arguments of Templeton and Morris (1998) in favour of DET, a switch from DET to SET was initially alleged to offer the same benefits that the earlier switch from multiple embryo transfers to DET had brought to the field: maintenance of pregnancy rates but reduction in multiple pregnancies (in this case, twin pregnancies). While some authorities still maintain that SET does not reduce pregnancy chances in comparison to DET (Moustafa *et al.*, 2008), a large majority of studies quite clearly demonstrates that SET reduces pregnancy rates to a significant degree in comparison to DET, thus requiring additional cycle activity to equalize pregnancy chances (Pandian *et al.*, 2005; Fiddelers, *et al.*, 2006; Van Montfoort *et al.*, 2006). Proponents of SET, however, still argue that additional cycle activity is a worthwhile price to pay because singleton pregnancies carry lower outcome risks (and therefore costs) than twin pregnancies.

This argument is, however, also statistically incorrect (Gleicher and Barad, 2008a). While nobody can argue that one twin pregnancy does not carry a higher risk than one singleton pregnancy, it is statistically incorrect not to correct risk comparisons for outcome. In other words, infertile couples (who, in a large majority, enter fertility therapy desirous of more than one child) achieve different benefits from twins and singleton births: in the former case they have two children, while in the latter they have only one child. Equalizing risk for outcome, therefore, means comparing risk of one twin pregnancy to two singleton pregnancies, not only to one pregnancy, as historically has been the practice of proponents of SET.

When this is done, risk profiles for twin deliveries are no longer higher (Gleicher and Barad, 2008a), thus depriving proponents of SET of any remaining argument in favour of this procedure, unless women are desirous of only one child or have obstetrical contraindications to the delivery of twin gestations. Additional clinical indications for SET may arise in the future. For example, if milder ovarian stimulation is proven to reduce aneuploidy rates (Weghofer *et al.*, 2008), SET may again increase in relative importance, since fewer embryos would be produced. However, as things stand today and as noted a number of years ago (Gleicher and Barad, 2006), SET appears to be indicated in only a very small minority of IVF patients.

The inappropriately wide introduction of PGS and SET into routine IVF practice offers convincing evidence that even seemingly very logical ideas in clinical medicine require experimental confirmation before their introduction into routine clinical practice (Ankum *et al.*, 2008). Quite obviously, very

well-meaning scientists initially considered PGS and SET to be such obvious improvements to routine IVF that formal statistical models and clinical trials appeared unnecessary before clinical utilization. In retrospect, they were incorrect. PGS and SET, therefore, still should be considered as experimental procedures until it is determined whether they have benefits in defined subpopulations of patients. As a universal modification of IVF practice patterns, neither one appears appropriate.

Patient entitlements

Patients who are advised to undergo PGS or SET may not be offered maximally obtainable pregnancy chances and therefore have to consent accordingly. Unfortunately, still without proper clinical trials, other major interventions into routine IVF practice are also already under way, often similarly propagated to patients without proper scientific underpinnings. These include the concepts of mild and minimal ovarian stimulation and/or natural-cycle IVF (Pelinck *et al.*, 2006, 2007; Matsuura *et al.*, 2008), which have been receiving increasing attention as being 'patient friendly IVF' and 'approximating the physiological conditions of the natural cycles'. Nygren (2007) even suggested in an opinion piece that the success of SET mandates it as a next step for further intervention into traditional IVF protocols, along the line of natural cycle IVF and/or soft stimulation. In contrast, Flisser *et al.* (2007), in our opinion correctly, recently argued against prematurely adopting these modifications to standard IVF procedures without adequate evidence of their competitiveness in outcomes with standard IVF procedures.

Conclusion

It appears to be time to reemphasize the physician's obligation to offer maximal treatment outcomes and, in the case of IVF, this means maximal pregnancy chances. IVF pregnancy rates have been steadily improving (Toner, 2002) and the large-scale introduction of untested practice patterns potentially endangers this trend. For routine infertility patients, IVF is now a mature and predictable procedure, with specific age-appropriate pregnancy expectations. Patients are entitled to these expectations and a clinician's first responsibility is to meet them.

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