The challenges and promise of reproductive medicine in the 21st century

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Abstract
The development of Assisted Reproductive Technology (ART) proved to be a disruptive innovation. In Vitro Fertilization (IVF), now in its third decade, vanquished barrenness forever, changed Reproductive Medicine as we knew it, and led to a Nobel Prize in Physiology and Medicine. What is more, IVF spawned numerous unanticipated breakthroughs and still does at breakneck speed. However, ART in general and IVF in particular were associated with one significant unintended consequence, that is, multiple births. Therein lies the challenge. The promise of IVF is harbored in the technology that was and is being developed to predict the reproductive success of the embryo-to-be transferred with an eye towards reducing the incidence of multiple births while increasing the overall efficacy of conception.

Key words: Assisted Reproductive Technology (ART), In Vitro Fertilization (IVF), reproductive medicine

The development of Assisted Reproductive Technology (ART) proved to be a disruptive innovation. In Vitro Fertilization (IVF), now in its third decade, vanquished barrenness forever, changed Reproductive Medicine as we knew it, and led to a Nobel Prize in physiology and medicine [1]. What is more, IVF spawned numerous unanticipated breakthroughs, and still does, at breakneck speed. However, ART in general and IVF in particular gave rise to one significant unintended consequence, that is, multiple births [2-4]. Therein lies the challenge.

The United States has witnessed a 7-fold increase in its national higher-order birth rate from 1967 (the proximate bookend of the modern era of fertility promotion) to 2012 (the last year for which reliable data are available) [2]. Although down 36% since a 1998 high, the national higher-order birth rate remains significantly increased (4.3-fold) relative to the 1967 benchmark [2]. During the same time frame, the United States has also witnessed a 2-fold increase in its national twin birth rate [2]. Although the annual growth of the national twin birth rate has slowed down substantially, it has yet to reverse course, that is, begin to decline [2]. It follows that for the foreseeable future, the United States stands to be a “Twin Nation.”

As such, this state of affairs is hardly surprising. Indeed, the national IVF twin birth rate has all but remained constant from 1997 to 2011 at approximately 400 per 10^3 live infants born [2]. Similarly, the national fraction of double embryo transfers has been increasing since 1997 to plateau in 2011 at 55% of all embryo transfers [2]. It stands to reason that this state of affairs will not improve until such time that the national single embryo transfer fraction will continue its rise beyond its 2011 level (21% of all embryo transfers) [2]. Above and beyond the preceding considerations, the national twin and higher-order birth rates have also been driven up by non-IVF fertility-promoting therapies such as ovulation induction and medicated Intra Uterine Insemination (IUI) [2, 6, 7]. Indeed, from 1997 to 2011, non-IVF technologies consistently exceeded IVF as contributors to the national twin birth rate [2]. By the same token, from 2004 to 2011, non-IVF technologies consistently exceeded IVF as contributors to the national higher-order birth rate [2]. Finally, consideration must also be given to the possibility that demographic elements may constitute a component in the multifactorial genesis of multiple births. In general, it is possible that increased maternal age and growing racial diversity are doing their part to drive up the national birth plurality rates [2].

To address the multiple births challenge, the utilization of ovulation induction and especially of medicated IUI may have to be curtailed. However, the real promise is harbored in the technology that was and is being developed to predict the reproductive success of the embryo-to-be transferred during IVF with an eye towards electively transferring no more than a single embryo (i.e. elective Single Embryo Transfer; eSET) and thereby reducing the incidence of multiple births while increasing the overall efficacy of conception [8]. In more ways than one, this future promise appears to be inextricably
linked to furthering the process of embryo selection thereby increasing the confidence of patient and provider in the reproductive success of eSET. Then and only then can one anticipate an all-out attenuation if not elimination of the multiple births epidemic [8].

One leading predictive contender is premised on the notion that morphokinetic patterns of early cellular embryonic division may be in a position to predict the likelihood of embryonic development to the blastocyst level [9]. More recent work raises the prospect that morphokinetic patterns of early cellular embryonic division may also be in a position to predict the likelihood of aneuploidy at the blastocyst level [10]. Subject to affirmative clinical trials, it is within the realm of possibility that this technology may become standard fare in the IVF management paradigm. Similar progress is being witnessed in the rapid establishment of the ploidy status of the blastocyst-to-be transferred by way of a trophoectodermal biopsy. Commonly known as Preimplantation Genetic Screening (PGS), this rapidly evolving technology is being debated and vetted at the time of this writing [11, 12].

Further down the line lies the promise of ovary-independent IVF, that is, the possibility that the oocytic lineage could be derived from a somatic cell. This byproduct of the discovery of the induced pluripotent stem cell (iPS) phenomenon relies on the in vitro coaxing of undifferentiated precursors into fertilizable oocytes [13]. Led by Kyoto-based Professor Saitou and his colleagues, this approach, presently demonstrable in rodents, stands to disrupt reproductive biology yet again with as yet unforeseen consequences.

Broadly viewed, the field of ART is in the midst of a transition. Challenges are being addressed and promises are being realized. There is no telling what the future holds though it will surely not be lacking in excitement.

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References