The multiple births epidemic: The growing role of superovulation and intrauterine insemination

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Abstract

Superovulation and Intrauterine Insemination (S/IUI) is emerging as a significant driver of the multiple births epidemic. Regrettably, multiple births attributable to S/IUI may not be entirely preventable. However, mitigation is possible if one accepts the proposition that low-dose (≤ 75IU) Gonadotropin, Clomiphene, and off label Letrozole regimens improve on the outcome of high-dose (≥ 150IU) Gonadotropin counterparts in the multiple births category and that per cycle pregnancy rates are comparable. It follows that high-dose Gonadotropin regimens must be used judiciously and that they be substituted by available alternatives whenever possible. For the foreseeable future, S/IUI is here to stay. In time however, S/IUI may well be superseded by In Vitro Fertilization at a point in time when the affordability of the latter is no longer rate limiting.

Key words: multiple birth epidemic, superovulation, intrauterine insemination

Superovulation and Intrauterine Insemination (S/IUI), as introduced by Dodson et al. [1], emerged as a leading therapeutic option for ovulatory infertile women. As recently as 2011, a Systematic Intervention Review of the Cochrane Database on ovarian stimulation protocols [2] concluded that while “robust evidence is lacking... gonadotrophins might be the most effective drugs when IUI is combined with ovarian hyperstimulation”. It follows that S/IUI constitutes a key component of contemporary infertility therapy which is being offered by generalists and reproductive endocrinologists alike. A tripartite process, S/IUI comprises superovulation, ovulation triggering, and intrauterine insemination (Fig. 1).

The superovulation component is carried out with Gonadotropins (native or recombinant), Clomiphene (a selective estrogen receptor modulator), off label Letrozole (a non-steroidal aromatase inhibitor), or combinations thereof. All of the agents in question have been shown to promote the growth and development of (frequently multiple) ovarian follicles. Ovulation triggering, usually the domain of Human Chorionic Gonadotropin, is generally timed by sonographic and/or hormonal monitoring. Intrauterine insemination is generally carried out within 48 hours after the administration of the ovulatory trigger.

For nations so affected, the multiple births epidemic is a matter of ongoing concern [3-7] consequent to the prospect of adverse perinatal outcomes [8, 9]. Regrettably, evolving experience suggests a growing role for S/IUI in the genesis of birth plurality. Indeed, use of high-dose (≥ 150 IU) Gonadotropin regimens has been shown to give rise to twin and high order pregnancy rates as high as 29 and 9%, respectively [10].

The very fact that S/IUI gives rise to multiple births is hardly surprising. However, documenting the relative contribution of S/IUI to the multiple births epidemic is far from trivial. In the US, the latter challenge is traceable to the absence of a national registry for S/IUI cycles the public reporting of which is not required. Stated differently, S/IUI cycles, unlike Assisted Reproductive Technology (ART; In Vitro Fertilization and Egg Donation) procedures (11-13), are not the subject of mandatory reporting and thus are not available for review and
analysis. It follows that the role of S/IUI in the multiple births epidemic of the US cannot be determined directly. Instead, multiple births referable to S/IUI must be imputed indirectly and in a fashion that is far from satisfactory. Moreover, multiple births attributable to S/IUI cannot be teased apart from those ascribable to Ovulation induction (OI) for which a public registry is similarly non-existent. Subject to these limitations, the Centers for Disease Control and Prevention (CDC) has undertaken to estimate the relative contribution of S/IUI and OI to the multiple births epidemic of the US [14-16]. Specifically, the CDC proceeded to subtract (from the national multiple births cohort) spontaneously conceived and ART-induced multiple births to arrive at the relative contribution of S/IUI and OI. Best estimates dating back to 1997 reveal S/IUI and OI to contribute in excess of 22% of the multiple births pool [16]. As such, these observations reveal an upward trend from 1997 at which time the contribution of S/IUI and OI was deemed to have reached 19% [14, 15].

Given that S/IUI is all about the release of more than a single fertilizable oocyte, the multiple births associated with S/IUI are unlikely to be entirely preventable. In fact, the risk of birth plurality for S/IUI is intrinsic and indeed anticipated. Comparable conclusions have been enunciated this very year by the Practice Committee of the American Society for Reproductive Medicine [17]. Note was also made of the fact that diligent imaging and hormonal tracking of S/IUI do not forestall gestational plurality. In other words, imaging and hormonal thresholds to guide the triggering of ovulation or the withholding thereof cannot be defined [17].

Although the birth plurality associated with S/IUI is not entirely preventable, mitigation constitutes a distinct possibility. In this context, serious consideration should be given to low-dose (≤75 IU) Gonadotropin regimens which have proven notable for the frequent absence of high order (but not twin) gestation [10]. Alternatively, use could be made of Clomiphene the record of which is similarly noteworthy for the virtual absence of high order (but not twin) gestation [10]. In addition, note must be made of the off label use of Letrozole for which no high order and no more than a few twin gestations have been reported [10]. Finally, mention must be made of the option of preovulatory ultrasound-guided aspiration of supernumerary follicles for which the cumulative record reveals multiple pregnancy rates of ≤10% [18-20]. In many of these cases, per cycle pregnancy rates proved comparable if not superior to those reported for high dose Gonadotropin regimens [10].

Taken together, current insights support the view that S/IUI is a significant contributor to the multiple births epidemic in the US and possibly elsewhere. In the special case of high-dose Gonadotropin regimens, note was made of twin and high order gestation rates in the range of 29 and 9%, respectively [10]. In addition, reports from the CDC (14-16) suggest that during the 1997-2005 interval, S/IUI and OI combined to account for > 20% of the US multiple births pool. Although multiple births ascribable to S/IUI cannot be entirely prevented, mitigation constitutes a distinct possibility. In this regard, significant promise rests with the deployment of low-dose Gonadotropin, Clomiphene, and off label Letrozole regimens. Stated differently, available alternatives may well harbor the potential to reduce the incidence of S/IUI-attributable multiple gestation, especially of the high order variety. It would thus appear prudent to recommend that high-dose Gonadotropin regimens be used judiciously and that emerging alternatives be increasingly utilized in their stead. Significantly, these conclusions appear compatible with those reached by a recent Systematic Intervention Review of the Cochrane Database [2] wherein the statement is made that, “...low dose protocols are advised since pregnancy rates do not differ from pregnancy rates which result from high dose regimen, whereas the chance to encounter...multiples and OHSS [Ovarian Hyperstimulation Syndrome] are limited with low dose gonadotrophins”.

Looking ahead, the prospect of additional rigorous randomized clinical trials must be given a thorough hearing. In this regard, mention must be made of the AMIGOS (Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation) trial wherein Gonadotropins, Clomiphene, and Letrozole are being compared and contrasted [21]. In addition, significant deliberations must be dedicated to the prospect of enhancing public reporting in the US thereby incorporating the clinical outcomes of S/IUI as is the case in the European Union [22]. Finally, consideration must be given to the possibility that S/IUI may be superseded by In Vitro Fertilization (an “IVF-only world”) at a point in time when affordability is no longer rate limiting. The strength of such scenario resides in the reality that multiple births outcomes can be far better controlled by the number of embryos transferred.

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References


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