Natural ovarian stimulation (NATOS): effectively natural

Given that the so-called "mild" ovarian stimulation procedures, together with their underlying die-hard ideology are, finally, running out of steam under the blows of evidence-based medicine and patient choices, the time has come to take over the concept of "natural" in reproductive care—this time, in the name of efficacy. Indeed, numbers in France indicate the cost of live birth through in vitro fertilization (IVF)-embryo transfer (ET) exceeds US$15,000-, mainly because per-cycle effectiveness of treatments remains low in France and patients often need to undergo repeated cycles to finally conceive. It becomes, therefore, mandatory to reduce the time to live birth in IVF-ET primarily acting by improving the efficacy of controlled ovarian stimulation (COS).

Whereas strong COS, in the era of agonist-triggered antagonist protocols, offers conspicuous advantages and security to patients, some older problems not only persist but may even have been amplified. On the one hand, by substantially increasing per-cycle oocyte and embryo availability, strong COS improves embryo selection for fresh ET and opens the possibility of achieving subsequent pregnancies through the cryopreservation of spare embryos. On the other hand, due to the multiplicity of preovulatory follicles, strong COS induces compulsory and unwanted alterations in the endocrine milieu that may negatively affect results. The most striking of them is the extremely high estradiol (E2) levels (over 10- to 15-fold the physiological range).

Possible Detrimental Effects of High Estradiol Levels on Embryo Quality

Recent studies indicate embryo competence, particularly assessed by blastocyst euploidy rate, remains unaffected by high E2 levels achieved in strong COS. Yet, the inherent ability of each patient to respond strongly or not to COS, which is itself a prognosis factor, may constitute a considerable bias to this analysis. In order to properly address this issue, it would be required to dissociate E2 production from the strength of COS which is unrealistic in conventional COS protocols. In addition, doubts on the harmlessness of high E2 levels on embryo quality have been raised by early investigations conducted in rodents. These studies demonstrated a progressive reduction of blastulation and embryo adhesion rates after the exposure of embryos to increasing E2 concentrations (1). These data cannot be simply brushed aside.

Possible Detrimental Effects of High E2 Levels on Uterine Receptivity

Similar picture here, uterine receptivity may be another possible collateral victim of high E2 levels often achieved by strong COS. And, as for the possible embryo alterations mentioned previously, it would be difficult to demonstrate a direct detrimental effect of excessive levels of this hormone on uterine receptivity since good prognosis patients are often strong responders. Therefore, mainly in these patients, subtle harmful effects of high E2 on uterine receptivity could remain undetected. Incidentally, high E2 levels have been associated to the presence of apoptotic bodies and DNA fragmentation in glandular cells of the human endometrium (2). In addition, among the hyper responder population, patients with lower E2 levels will be more often pregnant after IVF-ET (3). Another potential detrimental effect of high E2 levels is possibly targeted against the contractile activity of the myometrium. In previous studies, we demonstrated a hyper contractile uterus may hamper embryo implantation in IVF-ET and the myometrial activity is, at a large extent, regulated by ovarian steroids, in particular E2 and progesterone. During the follicular phase of the menstrual cycle, E2 stimulates uterine contraction frequency, probably to assist sperm transport and, after ovulation, progesterone exerts a remarkable utero-relaxing effect to facilitate the proper positioning of embryos in the uterine cavity and foster embryo implantation. We have previously observed that, in the presence of supraphysiologic E2 levels comparable to those obtained after COS, the myorelaxing action of progesterone is significantly altered, a phenomenon that may affect negatively embryo implantation (4).

Current Alternatives

To control the possible adverse effects of high E2 levels on IVF-ET outcome, some strategies have been used, in particular, separating the COS phase from ET phase by total embryo vitrification or attenuating E2 production with aromatase inhibitors. The "freeze-all" strategy allows the combination of an intense COS with a deferred uterine preparation for embryo implantation. Yet, the "freeze-all" approach is unable to preserve embryo quality from supraphysiologic E2 effects, requires efficient vitrification techniques and settings, and extends, by design, the time to live birth due to the deferred ET cycle. Another option for attenuating E2 production during COS is the use of aromatase inhibitors. Unfortunately, serum E2 levels achieved with the combination FSH-letrozole often exceed those observed in the menstrual cycle (3).

Natural Ovarian Stimulation

Aiming at developing new agendas for COS protocols, trying to together keep the advantages of strong egg production while eliminating possible drawbacks of high E2 levels, we elaborated the NATOS concept. The aim of NATOS is to dissociate the magnitude of E2 production from the intensity of multiple follicle development by keeping serum E2 levels within the physiological range. For obtaining this effect, we elected to virtually curtail endogenous LH levels with strong and frequent (1.5 mg/day) GnRH antagonist doses during the whole recombinant FSH administration course. Acting one stage upper than aromatase inhibition in the hormonal cascade that culminates in E2 production, NATOS reduces thecal androgen production to a minimum so that E2 production never rises beyond the "natural" range during the entire COS. After initial outstanding IVF-ET oucome obtained with this novel COH strategy, we are presently conducting a

multicentric randomized prospective trial to confirm superiority of NATOS over conventional GnRH antagonist protocols.

Conclusion

Definitely, there is something new under the sun of COS. NATOS may offer a promising alternative to both "freeze-all" and aromatase inhibition approaches for further improving effectiveness of strong COS. It appears to be a successful way for reconciling strong COS with some key events of the natural cycle, since peak E2 levels are even lower than those commonly observed with aromatase inhibitor co-treatment, remaining absolutely within the physiological range. This controlled hormonal environment is likely to produce positive effects on both embryo competence and uterine receptivity, while keeping strong egg production, which may explain the high pregnancy rates achieved. Further, NATOS differs from classical "LH-null" models, as hypophysectomized rodents or patients suffering from hypothalamic amenorrhea stimulated with FSH alone were clearly disappointing. This new COS protocol renders LH levels undetectable by strong daily GnRH antagonist doses, but probably not null, as illustrated by the marginal E2 production, which is, in turn, enough to proliferate the endometrium and ensure excellent IVF-ET outcome. Incidentally, NATOS challenges the need of significant LH activity during COS in normal responder patients. Finally, performing NATOS in alternative and less costly ways, possibly by associating GnRH antagonists to agonists, oral contraceptives, or aromatase inhibitors, may be also envisioned and should be tested in further studies.

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