Impact of ovarian stimulation with gonadotrophins on embryo aneuploidy

Sir,

We have read the article published in your journal by Taylor et al. (2014) with much interest. In this review the authors properly summarize the mechanisms, origins and incidence of chromosomal mosaicism in humans.

The review is rigorous, exhaustive and very well-documented, and therefore we congratulate the authors for their work. Nevertheless, we find that some relevant information about the external influences that could contribute to mosaicism and/or embryo aneuploidy is missing. Authors state that ‘hyperstimulation has been implicated in increased rates of cleavage stage aneuploidy’. We consider that this statement should not be so categorical as the potential deleterious effect of ovarian stimulation on oocyte and embryo quality is still the subject of lively debate.

We conducted the first prospective cohort study by comparing unstimulated and stimulated cycles in the same woman (Labarta et al., 2012). The intrasubject comparison showed a rate of aneuploidy of 34.8% (95% CI = 20.5–49.1) in the unstimulated cycle and 38.2% (95% CI = 30.5–45.8) in the stimulated cycle (risk difference = 3.4 (95% CI = –17.9 to 11.2)). No differences were observed for embryo quality and type of chromosomal abnormalities. We concluded that ovarian stimulation does not significantly raise the embryo aneuploidy rate in IVF-derived human embryos when compared with an unstimulated cycle.

The study was conducted in egg donors, younger than 35 years old with no previous ovarian stimulation treatments. The time frame between both unstimulated and stimulated cycles was a maximum of 3 months. The design of this study avoided some biases, such as impact of age on aneuploidy, intersubject variability, infertility background and different lab conditions between distinct IVF centres, such that we could analyse the net impact of gonadotrophins on embryo aneuploidy.

We were also able to analyse the largest sample of IVF-derived embryos from unstimulated cycles, and we observed an aneuploidy rate of 34.8%, which is in agreement with previously published data (Verpoest et al., 2008). These results suggest that embryo aneuploidies are present in human beings, even in the absence of ovarian stimulation, and that this could be the reason why fertility in humans is so ineffective.

These findings are supported by previous data showing that when comparing natural and stimulated cycles, no differences were observed in terms of cleavage capacity, embryo quality or incidence of aneuploidy in aborted fetuses.

Other studies have compared the effect of different doses of gonadotrophins—instead of natural versus stimulated cycles—on the rate of mosaicism and embryo aneuploidy. In infertile patients, it has been suggested that the use of gonadotrophins might raise the chromosomal abnormality rate in a dose-dependent manner, mainly due to an increased incidence of mosaicism (Baart et al., 2007). Yet in oocyte donors, our group observed that the incidence of mosaicism was similar, regardless of the doses of gonadotrophins used. However, the same study showed that when doses are small, but the number of oocytes obtained is similar to higher doses in the same egg donor, the incidence of mosaicism lowers (Rubio et al., 2010).

In summary, according to recent literature, it cannot be stated that ovarian stimulation with gonadotrophins may significantly increase the rate of embryo aneuploidy in patients without the negative effect of age acting as a confounding factor. Moreover, embryo aneuploidy is present even in unstimulated cycles, suggesting that either this is the real incidence in human beings or there are factors other than ovarian stimulation related with the IVF procedure which may increase this incidence in comparison with in vivo fertilization. Finally, mosaicism could be related with doses of gonadotrophins and this effect should be further studied.

References


E. Labarta*, E. Bosch and A. Pellicer
Department of Human Reproduction, Instituto Valenciano de Infertilidad (IVI), Valencia, Spain
*Correspondence address. E-mail: elena.labarta@ivi.es
doi:10.1093/humupd/dmu038
Advanced Access publication on July 10, 2014

Reply: Impact of ovarian stimulation with gonadotrophins on embryo aneuploidy

Sir,

We have received the comments by Labarta and colleagues and would like to address some of their concerns. First, we always appreciate the
opportunity to discuss/debate our work. Second, we recognize Labarta and colleagues’ continued work in the field of preimplantation genetics and certainly respect their opinion.

In terms of the impact of stimulation on preimplantation aneuploidy and mosaicism, it certainly is subject to a lively debate. Although evidence supports that gonadotrophins and ovarian hyperstimulation do not increase chromosomal aneuploidies in preimplantation embryos, the true incidence or consequences are unknown for a variety of reasons. First, although the study by Labarta et al. (2012) demonstrated no difference in aneuploidy between stimulated and unstimulated cycles, it is important to understand that their study (or any study) can control for intercycle differences. However, by utilizing the same patient in both cycles (both maternal and paternal), their study controlled for a wide range of factors and we applaud their study design. Second, the authors biopsied on Day 3 and performed fluorescent in situ hybridisation (FISH) to demonstrate similar aneuploidy rates between stimulated and unstimulated cycles. One could argue that Day 3 aneuploidy may not be predictive of chromosome copy number in the blastocyst, as mosaicism seems to be routine during the cleavage stage (Northrop et al., 2010). However, their study also examines aneuploidy by FISH, which has been shown to be incorrect (Treff et al., 2010). Although the error of the FISH technique is the same between the two groups, the true incidence of aneuploidy and mosaicism may be overstated, not only in their study, but in all studies pertaining to FISH.

Lastly, their study was performed in presumed fertile patients; it is quite possible that infertile patients act differently during hyperstimulation, something these authors correctly point out in their conclusions. However, research by Verpoest et al. (2008) suggests that infertile patients act similarly to fertile patients. We tend to favor the research by Labarta and colleagues demonstrating that gonadotrophins and ovarian hyperstimulation do not increase the risk of preimplantation aneuploidy or mosaicism. However, we felt it necessary simply to touch on this aspect of hyperstimulation and mosaicism, as the effects, or lack thereof, of ovarian hyperstimulation on preimplantation aneuploidy and mosaicism could be a review upon itself.

References


Tyl H. Taylor1,2,*, Susan A. Gitlin3 and Darren K. Griffin2

1Reproductive Endocrinology Associates of Charlotte, Charlotte, NC, USA
2University of Kent, Canterbury, UK
3Eastern Virginia Medical School, Norfolk, VA, USA

*Correspondence address. E-mail: tyltaylor@gmail.com
doi:10.1093/humupd/dmu039

Advanced Access publication on July 10, 2014