The two sides of the individualization of controlled ovarian stimulation

Dear Sir,
We read with great interest the article entitled ‘Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice’, published in Human Reproduction Update (La Marca and Sunkara, 2014). The authors performed a wide literature review over the issue of individualizing the ovarian stimulation in IVF cycles, according to predicting markers of ovarian response. Additionally, two different normograms are proposed for calculating the ideal FSH starting dose, based on age, serum FSH and either antral follicle count or serum anti-Müllerian hormone (AMH).

The choice of a particular regime of controlled ovarian stimulation (COS), with FSH doses based on individual characteristics sounds tempting, as individualization might be seen as the key to success in this step of assisted reproductive techniques. Authors justify that individualization may reduce the number of cycles cancelled due to inappropriate ovarian response (hyper or poor) and that this would lead to reduced costs and dropout rates. However, we should always keep in mind that there are two sides to every coin. The choice of an individualized scheme for each patient would demand additional exams to define the expected ovarian response. The need for more examinations, such as AMH, brings additional costs for the couples seeking treatment. If we consider that as many as 22% of couples incur catastrophic expenditure on ART (Dyer et al., 2013), adding costs might make infertility treatment even less accessible to infertile populations. Another important factor to consider is that additional examinations may also be responsible for additional stress for the couples involved. If we keep in mind that ~35% of dropouts after a single cycle are due to physical and psychological burden of the treatment (Verberg et al., 2008), the idea of adding even more stress, particularly for those who will be labelled as poor responders, might sound quite questionable.

Even considering that individualization of COS should be performed, we do not agree with the suggestion that women with predicted poor ovarian response should always be submitted to high-dose FSH regimens (La Marca and Sunkara, 2014). For this group of women, we should consider less expensive COS: a recent systematic review showed that COS with clomiphene citrate + low dose gonadotropins + GnRH antagonist resulted in a trend to better pregnancy rates and number of oocytes retrieved when compared with the classic high-dose FSH regime (Figureiredo et al., 2013). Reducing the costs for these women is even more important than for women with normal ovarian reserve: the pregnancy rate per cycle is much reduced and they will probably need several cycles before achieving pregnancy.

Conversely to COS individualization, some large centres are adopting a low cost, mild and fixed COS, regardless of age or expected ovarian response associated with a single embryo transfer policy (Kato et al., 2012). Using such an approach they reported acceptable pregnancy and live birth rates (obviously depending on women’s age), minimizing the costs and risks of assisted reproduction techniques.

In summary, we believe that when individualizing COS, low-cost regimens using clomiphene citrate should always be considered for women with predicted poor ovarian response. However, we think that individualization of COS still needs to be looked at with caution: examining assisted reproduction as a whole, and not only to the immediate results, the use of fixed, low cost and low-risk COS seems to be even more interesting.

References


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Reply: The two sides of the individualization of controlled ovarian stimulation

Dear Sir,

We thank Teixeira and Martins for their interest in our paper titled ‘Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice’ published in Human Reproduction Update (La Marca and Sunkara, 2014). We appreciate their agreement that individualization of ovarian stimulation sounds tempting and
appears objectively useful to the patient. Individualization can be associated with some increased costs but as discussed in the article it leads to increased safety and success. The cost for ovarian reserve assessment is \( \frac{1}{100} - \frac{1}{50} \) of the cost of an IVF cycle. The cost-effectiveness of routine anti-Müllerian hormone (AMH) measurement in all patients entering an IVF programme is a complex subject that cannot be addressed briefly. However, other aspects, such as total drug consumption, cycle cancellation, hospitalization rate due to ovarian hyperstimulation syndrome and live birth rate per started cycle have been demonstrated to be positively modified by the introduction of AMH measurement into clinical practice (Nelson et al., 2009; Yates et al., 2011). A recent computer-based simulation in a cohort of infertile women entering an IVF programme anticipated the relative cost-effective routine use of ovarian reserve markers in IVF practice. Two scenarios were compared: (i) up to three cycles of IVF with no ovarian reserve testing and (ii) up to three cycles of IVF with dose individualization of gonadotrophins based on ovarian reserve (Moolenaar et al., 2011). The cumulative live birth rate after 1 year was estimated to be 54.8% for the first scenario and 70.6% for the second scenario. Absolute costs per woman were estimated to be €6917 and €6678 for the first and second scenarios, respectively, suggesting a possible positive impact of ovarian reserve markers in daily clinical practice (Moolenaar et al., 2011). A second important aspect is related to the ongoing revision and improvement in the technology for AMH measurement. The increase in the reliability, accessibility and, more importantly, the upcoming automation of the assay may hopefully lead to a reduction in the AMH test cost to levels similar to other common hormones.

We would like to disagree with their statement that the AMH test may create stress to the couple. On the contrary we think that when women are well informed by clinicians regarding the anticipated risks with ovarian stimulation (risk of poor response and cancellation), this may in fact increase patient confidence, compliance and adherence to the ART treatment.

Regarding the treatment of poor responders, Teixeira and Martins disagree on the use of maximal stimulation in poor responders while proposing a mild stimulation. Our manuscript referred to women who were expected poor responders, in other words naïve patients expected posing a mild stimulation. Our manuscript referred to women who patient confidence, compliance and adherence to the ART treatment. On the contrary we think that when women are well informed by clinicians regarding the anticipated risks with ovarian stimulation (risk of poor response and cancellation), this may in fact increase patient confidence, compliance and adherence to the ART treatment. Alternatively, a mild stimulation may lead to a normal response in the second cycle in as high as 37.6% of women (Klinkert et al., 2004). We agree that there is currently no clear evidence on the use of either a maximal or minimal stimulation regimen as first choice among women with a severely low ovarian reserve or a previous poor response.

Finally, Teixeira and Martins proposed the use of low-cost, mild, fixed COS regardless of age or ovarian reserve for all women entering an IVF programme based on data from a retrospective study (Kato et al., 2012). This however needs to be substantiated by randomized controlled trials providing high-quality evidence. Individualization of drug selection and dosing has been an objective of physicians and health-care providers for many decades and is currently applied in a logical and clear way in daily medical practice in several other specialties; reproductive medicine should not be an exception to this universal law. Certainly personalized IVF is always in the best interests of the woman as we have detailed in our review.

References


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