The sub-optimal response to controlled ovarian stimulation: manageable or inevitable?

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In their opinion article within this issue of Human Reproduction, Polyzos and Sunkara propose to create a new, presumed clinically relevant, ovarian response category (Polyzos and Sunkara, 2015). Today, the poor responder is indisputably recognized as problematic, as the far below average prognosis for live birth, especially in women of higher age, sheds doubt on the added value of assisted reproductive technology (ART). Increasingly, the disadvantages of the high ovarian response become clear, with an uncertain safety profile and a trend towards sub-optimal live birth rates. Individualized management of these two patient groups has been the focus of a handful of studies and an ocean of opinions. We are not even close to evidence on how performance of ovarian stimulation will become optimized in terms of efficacy, costs and safety (Harrison et al., 2001; Popovic-Todorovic et al., 2003; Klinkert et al., 2005; Lekamge et al., 2008; Jayaprakasan et al., 2010; Olivennes et al., 2015). The reason is that only two RCTs on the subject have been executed (Popovic-Todorovic et al., 2003; Olivennes et al., 2015), while at the same time reviews with individualization algorithms have seen the light, without a solid scientific basis (La Marca et al., 2014).

What will the clinical significance be of the suboptimal responder group, defined as producing oocyte numbers in the range of 4–9. The sub-optimality in this specific response group has been suggested from large database studies as well as systematic reviews on ART outcome predictors. The estimated 20–50% reduction in the prospects for a live birth occurring in this group is believed to become reversed by changes in the ovarian stimulation treatment strategy, transforming the sub-optimal responder into the so called optimal responder, defined as obtaining 10–15 oocytes at retrieval.

The key question here is why the suboptimal responder has ‘suboptimal’ live birth prospects from the eggs that she did deliver to the IVF lab? It is certainly the quality distribution of these oocytes that will play the major role. While counting follicles and eggs is easy, assessing their quality is notoriously difficult. Indeed, identified markers for successful outcome in ART are egg number and female age (Sunkara et al., 2011a,b; Broer et al., 2013; van Loendersloot et al., 2010), but also duration and type of infertility. From studies on the ploidy status of blastocyst stage embryos it was demonstrated that, within female age categories, there is a stable proportion of euploid embryos, independent of the number of eggs obtained. This implies that having more eggs may allow for a better prospect of a live birth, as the chance of having at least one euploid embryo will increase with number (Ata et al., 2012).

Clinical observations, however, create a different story. In a recent re-combinant FSH dose finding study, a convincing dose–response relation was demonstrated, with higher FSH dose levels creating a linear increase in the number of oocytes retrieved (Arce et al., 2014). Surprisingly, with increasing numbers of eggs, no effect was seen on the absolute number of good quality blastocysts developing. Even more so, the cumulative live birth rates (frozen embryos included) did not show any increase when having more oocytes available. Several other studies have suggested that squeezing out all oocytes instead of a handful will only add poor quality eggs to the palette (Kok et al., 2006; Heijnen et al., 2007; Sterrenburg et al., 2011). The important question therefore remains whether the ‘sub-optimal’ responder has too few eggs, or is inherently different from the ‘optimal’ responder at the level of oocyte quality. The answer may be the necessary step before launching a new clinical entity, which in fact may be just a part of nature’s fecundity variation.

If we put aside the notion that the true meaning of having only 4–9 oocytes is unknown, we may wonder what chance the sub-optimal responder will stand to become normal. Let us for a moment look at the expectations that we may have, based on current evidence. Daily dosages of FSH in the range of 150–225 IU create maximal stimulation in our patients, in low, normal as well as high responders (Sterrenburg et al., 2011). Going up to a 300 IU dosage will not create more oocytes (Jayaprakasan et al., 2010). Current knowledge on patients with a supposed reduced follicle FSH sensitivity strongly indicates that an adjusted FSH dosage may yield a few more oocytes, but no better pregnancy rates (Behre et al., 2005). Studies on adjuvant therapies using LH, androgens, growth hormone or aromatase inhibitors in poor or normal responders have so far yielded only conflicting or confusing results (Mochtar et al., 2008; Sunkara et al., 2011a,b; Lehert et al., 2014; Nardo et al., 2015). With these facts in mind we may refrain from over-optimism on the tools to transform the sub-optimal responder.
Therefore, in conclusion, we may declare the new ‘sub-optimal’ response group as a distinct entity, we may search and find a strategy that will improve oocyte yield, and we may even perform the comparative trial to demonstrate the concept that indeed ‘more is better’. But, we may also wait for the results of the Optimist trial, as the sub-optimal responder group constitutes a separate randomized study arm (van Tilborg et al., 2012). If an elevated FSH dose in this patient group will prove ineffective, we may better focus on those research fields in reproductive medicine that hold better promise.

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