Are too many eggs truly too many?

It should come as no surprise that an endeavor as sophisticated as assisted reproduction becomes more complicated over time. Historically, in vitro fertilization (IVF) meant stimulation, retrieval, insemination, embryo culture, and transfer in a single cycle. This progression was commonly complicated by multiple gestation and, less frequently, ovarian hyperstimulation syndrome (OHSS). Pregnancy rates were a fraction of what they are today. Innovations, including extended embryo culture, gonadotropin-releasing hormone (GnRH) agonist triggering, comprehensive preimplantation genetic screening, vitrification, and single-embryo transfer, have heralded a transformation of fertility treatment with minimal associated risk. Accordingly, it is time to revisit and reconsider our dogmatic impressions of IVF, as the conventional wisdom of the past may not apply to the present.

The study by Polyzos et al. (1) moves toward simultaneously confirming and upending one such conventional understanding. Controlled ovarian hyperstimulation (COH), a hallmark of IVF, aims to provide multiple multiphase-II oocytes in a single retrieval. To date, the optimal egg yield remains unknown. It is clear that a poor response to COH is associated with reduced live-birth rates (LBR), and a lower LBR has also been associated with excessive oocyte yield. Most of the literature concerning the likelihood of pregnancy as a function of egg yield suggests a Gaussian distribution. Until recently, data support that excessive yields do not improve pregnancy rates and may in fact significantly increase the potential for complications, specifically OHSS (2, 3).

The increased risk of OHSS after a robust response is obvious, but it is uncertain why pregnancy rates may be negatively impacted by high egg yields. Clearly, high yields are associated with markedly elevated estradiol levels and premature rises in progesterone. These phenomena may affect the maturation progression of the endometrium or the developmental integrity of oocytes.

Prior reports relying on population data support the concept of a bell-shaped curve when relating egg yield to LBR (2, 3). Polyzos et al. (1) provide a much needed elaboration on this relationship. The concept that high egg yield negatively influences LBR is largely derived from data on fresh embryo transfers (2, 3). By contrast, Polyzos et al. have evaluated the outcomes of nearly 15,000 patients and included the cumulative rates from both fresh and subsequent frozen cycles.

Their study was conducted between 2009 and 2014 when embryos were vitrified with a potential for a freeze all cycle. In addition, GnRH agonists were used in at-risk patients to induce oocyte maturation (a technique largely absent from COS before 2011). Both these strategies could negatively impact fresh cycle pregnancy rates, but their inclusion allows for the assessment of their potential influence on frozen pregnancy rates and OHSS incidence. They report that close to 15% of fresh cycles were cancelled, ~5% for poor embryo quality and 10% for a freeze-all strategy. Such practices would influence outcomes at the margins of egg yield, helping to shape the Gaussian distribution of LBR. Accordingly, they found that beyond seven oocytes the LBR held steady in the fresh cycle until 20 oocytes, beyond which the LBR dropped.

Beyond 20 oocytes they noted that a vitrify-all strategy was employed 42% of the time. This cancellation rate would negatively influence both LBR and OHSS incidence in the fresh cycle. Although the OHSS incidence reached 3% in the >25 oocyte group, the incidence of OHSS would likely have been a great deal higher without the use of a vitrify-all strategy in at-risk patients. In addition, this strategy negatively influenced the pregnancy rate in the fresh cycle. However, the vitrify-all strategy did not negatively influence the cumulative LBR. In fact, they found that when combining fresh and frozen transfers, the more oocytes retrieved, the greater the likelihood of achieving a live birth. The cumulative LBR increased steadily as a function of egg yield, reaching a maximum of 70% when >25 oocytes were retrieved. This finding held true across all age groups and was independent of other factors.

The findings of Polyzos and colleagues run counter to those presented by Steward et al. (2) and Sunkara et al. (3). These two large population-based studies both concluded that beyond 15 oocytes the pregnancy rates declined and OHSS rates increased. Because these studies were conducted before 2011—before the widespread use of agonist triggers and cryopreserve-all strategies—it is not surprising that they were limited to fresh cycles. Restricting the analysis to fresh cycles, however, precluded the ability to assess the true impact of high egg yield on birth rates (2, 3).

Polyzos and colleagues offer a more comprehensive assessment, demonstrating that high egg yield does not appear to compromise the quality of vitrifiable embryos. They show that, although a robust stimulation is associated with OHSS, avoiding a fresh transfer in a high-yield scenario does not compromise the pregnancy likelihood in a frozen cycle. Frozen embryo transfers derived from high-yield cycles yielded a high LBR. Furthermore, steering clear of hCG for triggering or luteal support precluded OHSS.

The data they have presented provide reassurance that a high yield may not adversely impact the cumulative LBR, but it must be noted that Polyzos et al. included only antagonist protocols; their findings may not generalize to agonist protocols. Further, Polyzos et al. studied a young, prognostically favorable population. The study contained a disproportionately high number of patients undergoing treatment for male factor infertility and undergoing their first IVF cycle. Such prognostically favored patients may yield hardier oocytes that are more capable of adapting to robust COH. Because such a large percentage of high responders underwent a freeze-all strategy, a better understanding of the impact of a robust response on the endometrium cannot be obtained from the data presented.

Polyzos et al. draw similar, albeit more pronounced, conclusions as Magnusson et al. (4), who reported earlier this year. Magnusson et al. noted that the cumulative LBR increased to ~46% at 20 oocytes and then remained steady. Like Polyzos et al., Magnusson et al. noted an increased LBR beyond 20 oocytes for frozen embryo transfer cycles. The Magnusson study also differed from that of Polyzos in not being limited to GnRH antagonist cycles, in being more prognostically diverse, in including fewer freeze-all cycles, and in including an older population. All may explain why a linear relationship between egg yield and cumulative LBR was not seen by Magnusson.et al. beyond 20 oocytes (1, 4).

It should be noted that, as in the investigation by Polyzos et al., previous large studies have demonstrated a plateau in pregnancy rates for fresh cycles beyond seven to eight oocytes (2–4). This would suggest that there is no need to stimulate beyond this number. While this may be true, the question still remains as to the impact of hyperresponse on pregnancy outcomes. The Polyzos study suggests that cumulative LBR is not compromised and that a cryo-all strategy is warranted following a hyper-response. Many have argued for mild stimulation, but despite all attempts to prevent them, unpredictable hyperresponses do occur. Accordingly, the study by Polyzos et al. emphasizes that this can be managed safely without compromising the desired outcome. In no way should their findings be interpreted as a rationale for aggressively stimulating patients. When confronted by "too many," Polyzos et al. provide us with reassurance that pregnancy rates can be maintained while OHSS is minimized.

Ioanna Comstock, M.D.
David Frankfurter, M.D.
Department of Obstetrics and Gynecology, George Washington University, Washington, DC

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