# Does cumulative live birth plateau beyond a certain ovarian response?

Currently, patients undergoing in vitro fertilization (IVF) demand the process be optimized so their goal is achieved after a single cycle. The outcome of the ovarian stimulation procedure, from the perspectives of efficacy and safety, is crucial to reach this goal through the harvest of an optimal number of oocytes while avoiding such complications as ovarian hyperstimulation syndrome (OHSS). An interesting debate on whether the live-birth rate (LBR) plateaus beyond a certain number of oocytes retrieved is currently ongoing. While there is a general agreement regarding this event when only the fresh embryo transfer is considered, much more controversy has been generated recently when the cumulative outcome (i.e., including pregnancies achieved with the transfer of super numerous frozen embryos) is discussed.

There is strong evidence that the probability of achieving a live birth after a fresh embryo transfer is maximized if approximately 15 oocytes are retrieved (1). Moreover, higher responses showed slightly lower success rates, and a significantly increased risk of OHSS. The reasons explaining this event have been attributed to an altered endometrial milieu, that would lead to impaired endometrial receptivity. Less clear is if oocyte quality is also negatively affected.

On the other hand, contradictory results have been reported when the relationship between ovarian response and the cumulative LBR (cLBR) has been analyzed. While a large amount od data obtained from the British register suggests the average cLBR remains flat beyond an oocyte yield of 15 (2), several studies show that the higher the ovarian response, the higher the cLBR. Of relevance, a very large and recent study (3) that included individual patient analysis of almost 15,000 gonadotropin-releasing hormone (GnRH) antagonist cycles, showed that the cumulative probability of achieving a live birth does not plateau at any level of ovarian response, reaching in the extreme high response (> 35 oocytes) values above 75%.

What could be the reasons behind these different findings? Without question, the factor with a stronger impact on this relationship (cLBR by ovarian response) might be the quality of the cryopreservation programs. It is obvious that if survival rates to warming are sub-optimal, and implantation rates of the thawed embryos are low, the added value of the surplus embryos obtained in high responses is very limited. On the contrary, vitrification programs with survival rates higher than 90% and equal implantation rates than the fresh embryos, provide a very useful strategy to increase the cumulative LBR. This might be the reason why, while data obtained from large registers in which all types and qualities of cryopreservation programs are included, are unable to show an increased cumulative outcome in high responders, those originated in one or only a few good quality programs provide very different findings. Therefore, it would be highly recommendable that, when reporting on cLBR, the mean survival rate to warming and the implantation rate of the thawed embryos were described. Another possible reason to explain these differences could be behind the ovarian stimulation strategy. Those protocols aiming for mild responses, cause very few high responses and therefore short samples to draw strong conclusions.

Some authors have suggested that a high ovarian response might be also linked to an impaired oocyte and embryo quality, which leads to the hypothesis that beyond a certain ovarian response, no more good quality embryos can be obtained (4). However, the biological events explaining why those oocytes obtained after high responses could be less competent are not fully demonstrated. Indeed, it has been recently published that, in the context of oocyte donation, the number of euploid blastocysts available for transfer increases in parallel to the number of oocytes obtained (5), which ultimately leads to an increased cLBR.

Given the considerations mentioned, we believe that while mild ovarian responses might be enough for having a good chance of pregnancy in a fresh embryo, the optimization of an IVF cycle for a given patient involves an appropriate stimulation protocol able to maximize the ovarian response in those women in whom their ovarian reserve allows for it. This implies the use of GnRH antagonist protocols, with GnRH agonist triggering and freeze-all policy to avoid OHSS on one hand, and last generation cryopreservation programs with embryo vitrification on the other. Of course, clinical judgement to avoid life-threatening situations is also mandatory. This approach improves the cLBR per pick-up, and therefore diminishes the number of ovarian stimulation cycles a patient may need to undergo in order to fulfil her family building.

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