

Fertility preservation in women with endometriosis: speculations are finally over, the time for real data is initiated



In this issue of *Fertility and Sterility*, Cobo et al. (1) present a case series of women with endometriosis undergoing fertility preservation. Specifically, they report on 1,044 women who were diagnosed with endometriosis and who decided to bank their oocytes. The most striking result of this contribution is the high rate of women coming back to thaw their gametes (43%). Considering that this rate is expected to increase further by extending the length of follow-up, one may reasonably infer that the ultimate number needed to be treated will be below 2. Noteworthy, if we also consider the high reported rate of success associated with the procedure (46% of those who thawed their oocytes had a live birth), the number needed to be treated for a live birth would be about 5 ($100 / 0.43 * 0.46$). At face value, these numbers appear very attractive. Cobo et al. (1) should be commended for this impressive and pivotal study.

During the past two decades, a growing and consistent body of evidence has documented the detrimental effects of surgery for ovarian endometriosis. As a result, indications for surgery have shrunk (2). In this scenario, it is also not surprising that the issue of fertility preservation in women with endometriomas has received growing attention (3). Given the high rate of infertility associated to the disease, the interest has spread beyond ovarian endometriomas and has extended to endometriosis in general (if a woman will ultimately need in vitro fertilization procedures, it would be better to store eggs at a younger age). However, at present, evidence has been extremely limited (4). Before the contribution of Cobo et al. (1), few case reports and small case series were published (4). The debate on the opportunity to perform fertility preservation in women with endometriosis was theoretical. In this context, the article by Cobo et al. (1) represents a milestone on this important argument. After years of speculations, we finally have more solid data on which to develop thoughts and discussions.

Systematically recommending oocyte banking in women with endometriosis is premature at this point in time. Endometriosis is a relatively common disease, and we need more robust evidence before a plea for fertility preservation in affected women is indicated. Egg banking is expensive and exposes women to some clinical risks. Advocating for systematic fertility preservation in affected women can cause wastage of resources and exposure of patients to undue risks. There is the need for robust cost-effectiveness and cost-beneficial analyses. In this context, one of the most crucial points is disentangling the magnitude of the benefit. Cobo et al. (1) reported that 43% of women thawed their eggs and 46% of them achieved a live birth. However, these rates do not represent the real effectiveness. We cannot disentangle the proportion of women who would have achieved a

pregnancy with a fresh cycle after an in vitro fertilization procedure, thus without egg banking. The focus should be on the incremental benefit, not on the mere rate of achieved live births. Of relevance is that, in the study of Cobo et al. (1), 39% of the women who failed to become pregnant with frozen eggs and who subsequently continued with fresh cycles achieved a pregnancy. The real benefit that we have to extrapolate is the absolute difference in terms of live births between women who stored their eggs and those who did not. The study by Cobo et al. (1) is not informative on that point. In addition, one has to emphasize that the high rate of patients thawing their eggs (43%) and the short period of time between storing and thawing (a mean time of only 1.5 years) suggest that a large proportion of the included women did not undergo proper fertility preservation but, conversely, the egg freezing was part of a strategy of infertility treatment. Therefore they may have stored their eggs once they were already infertile but had to undergo surgery. This is clearly recognized by Cobo et al. (1) in their discussion. Inferring the rate of use documented in this study to the more general population of women with endometriosis who are not interested in pregnancy seeking at the time of diagnosis may overestimate the benefits of fertility preservation.

Several other related issues remain to be addressed. In our opinion, one of the most critical issues is identifying women with endometriosis who have higher chances to be infertile in their future. This would consent to restrict the recommendation for oocyte freezing to the subgroup of women with the highest chances of thawing their eggs, actually improving the cost-beneficial balance. Some validated tools are available to predict pregnancy after surgery (5). However, they are based on surgical findings and they are validated only for women who have had surgery and start seeking pregnancy immediately after surgery. We would conversely need an algorithm to be used before surgery (relying on symptoms and imaging information) that could also provide reliable prediction for future fertility (to properly counsel also young women who are not yet interested in childbearing).

In conclusion, we would really like to thank Cobo et al. (1) for their contribution, also on behalf of the whole scientific community and of women with the disease. The first stone is laid. However, there is now the need to build a robust castle. The ultimate aim is identifying in advance women who will really benefit from fertility preservation to render oocyte freezing cost beneficial. This step is essential for the public health system or insurance coverage and thus to avoid inequities.

Edgardo Somigliana, M.D., Ph.D.

Paolo Vercellini, M.D.

Department of Clinical Sciences and Community Health,
Università degli Studi di Milano and Fondazione IRCCS Ca'
Granda Ospedale Maggiore Policlinico, Milan, Italy

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