

**Fertility preservation in women with endometriosis.
Speculations are finally over, the time for real data has initiated.**

Edgardo SOMIGLIANA, MD-PhD ^a

Paolo VERCELLINI, MD ^a

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

To whom correspondence should be addressed

Edgardo SOMIGLIANA

Infertility Unit – Fondazione Ca' Granda, Ospedale Maggiore Policlinico

Via M. Fanti, 6 - 20122 - Milan - Italy

Phone: +39-0255034304

Email: edgardo.somigliana@unimi.it

In this issue of *Fertility and Sterility*, Cobo *et al.* present a huge case series of women with endometriosis undergoing fertility preservation (1). 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 (NNT) will be below 2. Noteworthy, if we also consider the high reported rate of success of the procedure (46% of those who thawed their oocytes had a live birth), the NNT for a live birth would be about 5 ($100 / 0.43 * 0.46$). At prima faces, these NNTs appears very attractive. The authors should be commended for this impressive and pivotal study.

Over the last two decades, a growing and consistent body of evidence has documented the detrimental effects of surgery for ovarian endometriomas. As a result, indications to 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). To note, 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 IVF, it would be obviously better to store eggs at a younger age). However, up to now, evidence has been extremely limited (4). Indeed, prior to the contribution of Cobo *et al.* (1), only few case reports and small case series were published (4). The debate on the opportunity to perform fertility preservation in women with endometriosis was inevitably theoretical. In this context, the paper from Cobo *et al.* represents a milestone on this important argument. After years of speculations, we finally have more solid data on which developing thoughts and discussions.

On the other hand, systematically recommending oocytes banking in women with endometriosis is premature. Endometriosis is a relatively common disease and we need more robust evidence prior to plea for fertility preservation in affected women. 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 mandatory need for robust cost-effectiveness and cost-beneficial analyses. In this context, one of the most crucial point is disentangling the magnitude of the benefit. Cobo *et al.* reported that 43% thawed their eggs and 46% of them achieved a live birth. However, these rates do not represent the real effectiveness. Indeed, we cannot disentangle the proportion of women who would have achieved anyhow the pregnancy with a post-surgical fresh cycle, thus without egg banking. The focus should be on the incremental benefit, not on the mere rate of achieved live births. Of relevance here is that, in the study of Cobo *et al.*, 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 of Cobo *et al.* is not informative on this 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. In other words, they may have stored their eggs once they were already infertile but had to undergo surgery. This is clearly recognized by the authors themselves in the discussion. Infer the rate of use observed in these women to the more general population of women with endometriosis who are not interested in pregnancy seeking at the time of diagnosis may over-estimate the benefits of fertility preservation.

Several other related issues remain to be addressed. In our opinion, one of the most critical is identifying women with endometriosis who have higher chances to be infertile in their future. This would consent to restrict the recommendation for oocytes 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 operated women who 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 (in order to properly counsel also young women who are not yet interested in childbearing).

In conclusion, we would really like to thank Cobo *et al.* 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 in order to render oocytes freezing cost-beneficial. This step is essential to claim for public health system or insurance coverage and thus to avoid inequities.

References

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