

Ovarian endometriosis and fertility preservation

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Endometriosis is one of the most frequently encountered benign diseases in gynecology. Complete resolution of endometriosis is not yet possible, but therapy has three major objectives: i) to preserve and improve fertility; ii) to reduce pain; and iii) to delay recurrence. We will focus on fertility preservation in women with severe endometriosis, including ovarian endometriosis.

How to safeguard fertility during surgery for endometriosis

The correct surgical approach: laparoscopic management of endometriomas using a combined technique of excisional and ablative surgery

The main question we need to address is should we favor surgery or IVF as a first-line approach for ovarian endometrioma-related infertility? We advocate surgery, having demonstrated that endometrioma formation may cause local inflammation, giving rise to structural alterations to the ovarian cortex that manifest as massive fibrosis and loss of cortex-specific stroma required to maintain follicular nests. Hence, subsequent dysregulation of folliculogenesis often results in 'burnout' of the stockpile of dormant follicles (Figure 1). However, there are arguments to consider and risks to weigh up in any discussion of the proposed options.

There are two main risks associated with surgical treatment of endometriomas: 1) the risk of excessive surgery (removal or destruction of normal ovarian cortex together with the endometrioma), resulting in a diminished ovarian reserve; and 2) the risk of incomplete surgery (with subsequent early recurrence of endometriomas). To overcome these potential problems, we developed an approach that combines the techniques of cystectomy and ablative surgery. This allows us to take the best elements from both, while avoiding the corresponding risks (excessive surgery or incomplete surgery respectively). After identifying the correct plane of cleavage, the inner lining of the cyst is stripped from normal ovarian tissue. Upon approaching the hilus where the ovarian tissue is more functional, partial cystectomy is performed, removing 80-90% of the cyst. After this first step (partial cystectomy), the ablative technique (CO2 laser, PlasmaJet) is applied to vaporize the remaining 10-20% of the endometrioma close to the hilus.

Autotransplantation of fresh human ovarian tissue in endometriosis patients

When radical treatment (oophorectomy) is needed, but also if there is a risk of recurrence after conservative treatment, immediate autotransplantation of healthy ovarian tissue should be seriously contemplated. Where appropriate, fresh ovarian cortex may also be

orthotopically transplanted to the heterolateral ovary according to the following technique (Figure 2):

- Normal residual cortex is dissected from endometriotic tissue (in the peritoneal cavity).
- As much medullary tissue as possible is removed from the cortex.
- The antihilar region of the heterolateral ovary is opened.
- Strips of cortical tissue are sutured to the decorticated medulla, as previously described, with the goal of increasing the follicular ovarian reserve of the heterolateral ovary.

How to preserve fertility in women at risk of premature ovarian insufficiency due to severe and recurrent endometriosis

In patients at risk of premature ovarian insufficiency, several options are currently available to preserve their fertility, including oocyte vitrification and ovarian tissue cryopreservation.

Vitrification of oocytes

This technique may be considered a good choice for patients affected by endometriosis because it is less invasive than cryopreservation of ovarian tissue, so there is no risk of future depletion of the ovarian reserve due to the procedure. The process of cryopreservation (vitrification) of oocytes may require several cycles of ovarian stimulation in order to collect enough oocytes (≥ 10), particularly if the ovarian reserve is already compromised. It is also important to point out that successful oocyte vitrification is related to age. Indeed, a recent study by Cobo et al. found that the cumulative live birth rate significantly decreased in women over 35 years of age, suggesting that patients with endometriosis should be encouraged to freeze their oocytes at a younger age in order to increase their chances of future conception.

Cryopreservation of ovarian tissue and transplantation

Cryopreservation of healthy ovarian tissue obtained from women undergoing surgery for severe ovarian endometriosis is another reliable way of safeguarding fertility, especially in case of recurrence. Indeed, orthotopic autotransplantation of cryopreserved ovarian cortex has proved highly efficient, leading to restoration of ovarian function and pregnancy, with over 150 live births reported to date. Revascularization remains a crucial issue and research should be undertaken to find ways of decreasing the period of hypoxia after graft reimplantation. To this end, our group recently published an interesting two-step ovarian tissue transplantation approach using adipose tissue-derived stem cells to prepare the peritoneal grafting site 14 days prior to ovarian tissue transplantation.

Risks

In case of microscopic endometriotic foci in apparently normal ovarian tissue, reimplantation of fresh or cryopreserved ovarian tissue may lead to disease recurrence. Nevertheless, the risk is probably very low, as only the cortex of this apparently healthy tissue is grafted.

Conclusions

In case of severe endometriosis and/or recurrent endometriomas, normal residual ovarian tissue and/or ovarian vascularization may be compromised. Therefore, two main fertility preservation options should be considered: 1) oocyte vitrification after controlled ovarian stimulation (to obtain 10-20 oocytes); and/or 2) reimplantation of fresh or frozen ovarian tissue. Ovarian cortex cryopreservation should be offered to all women at high risk of severe recurrent ovarian endometriomas.

Figures

Figure 1: The 'burnout' hypothesis may explain the mechanism partly responsible for the reduced ovarian reserve in women with endometriomas. Formation of endometriomas may cause focal inflammation in ovarian cortex. This inflammation could result in structural alterations to the cortex, which manifest as massive fibrosis and loss of cortex-specific stroma that maintains follicular nests. Focal loss of follicular density may be associated with a vicious circle of dysregulated folliculogenesis that eventually results in burnout of the stockpile of dormant follicles. Modified from Kitajima et al (Fertil Steril, 2014). AMH: anti-Müllerian hormone.

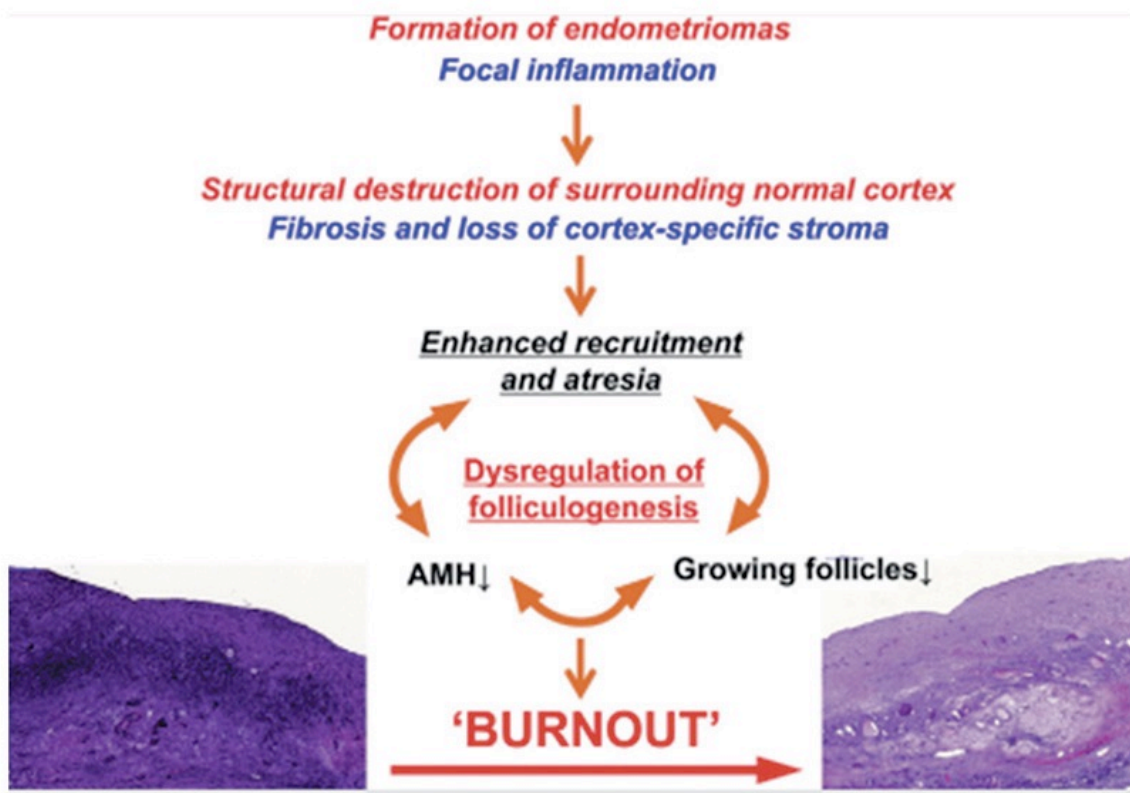


Figure 2: Autotransplantation of fresh ovarian tissue in endometriosis patients. After oophorectomy (1), strips of healthy ovarian cortex are dissected from the endometriotic tissue (2, 3) and grafted to the hetero-lateral ovary (4).

