Fertility preservation in women with endometriosis: for all, for some, for none?

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ABSTRACT: The increasing confidence with the techniques of oocyte and ovarian cortex freezing has prompted their potential use for patient categories other than those at risk of early menopause due to cancer treatments. Women affected by every iatrogenic or pathologic condition known to compromise ovarian function severely have been considered as potential candidates for fertility preservation. Among them, women with endometriosis may represent a particularly suitable group since they are at increased risk of premature ovarian exhaustion and about half of them will experience infertility. Based on the currently available notions on the intricate relationships between endometriosis, infertility and damage to the ovarian reserve, we speculate that fertility preservation may be of interest for women with endometriosis, in particular for those with bilateral unoperated endometriomas and for those who previously had excision of unilateral endometriomas and require surgery for a contralateral recurrence. Young age at diagnosis may be an independent but pivotal additional factor to be taken into consideration in the balance of the pros and cons of fertility preservation. On the other hand, we argue against the introduction of fertility preservation for endometriosis in routine clinical practice. To date, only few cases have been reported and there are insufficient data for robust cost-utility analyses. It is noteworthy that endometriosis is a relatively common disease and systematically including affected women in a fertility preservation program would have profound clinical, logistic and financial effects. More clinical data and in-depth economic analysis are imperative prior to recommending its routine use.

Key words: endometriosis / fertility preservation / endometrioma

Introduction

Oocyte cryopreservation is a recently developed technology whose use is rapidly increasing (Donnez and Dolmans, 2013; Chian et al., 2014; de Vos et al., 2014; Stoop et al., 2014). The advent of reliable vitrification protocols has simplified and improved the procedure (Glujovsky et al., 2014). Recent meta-analyses show comparable fertilization, cleavage and clinical pregnancy rates between vitrified and fresh oocytes. Even if the ongoing pregnancy rate is mildly reduced in the vitrified group, the results obtained highlight the scientific excellence achieved over the last decade and overall suggest that oocyte cryopreservation is an effective procedure (Cobo and Diaz, 2011; Cil et al., 2013; Potdar et al., 2014). In women requiring fertility preservation prior to exposure to gonadotoxic treatments, this technique is currently replacing embryo freezing using partner or donor gametes because of its indisputable ethical advantages (de Vos et al., 2014). The recent remarkable improvements of the freezing methods have also allowed the development of ovarian cortex cryopreservation. Even if this latter technique should still be considered experimental, it is increasingly used in women for whom established methods of fertility preservation cannot be applied or a delay in the initiation of gonadotoxic treatments is not possible (de Vos et al., 2014). Some authors even foresee that this technique may become the first-line option in the near future (Stoop et al., 2014).

It is actually this increasing confidence with the techniques of oocytes and ovarian cortex freezing that has prompted their potential use for patient categories other than those at risk of early menopause due to cancer treatments (de Vos et al., 2014; Stoop et al., 2014). Indeed, patients affected by every iatrogenic or pathologic condition known to compromise ovarian function severely have been considered as potential candidates for fertility preservation. Among them, women with endometriosis may represent a particularly suitable group since they are known to be at increased risk of infertility and earlier impairment of...
the ovarian reserve (de Ziegler et al., 2010; Vercellini et al., 2014). It is noteworthy that endometriosis is also a chronic disorder with a significant tendency to recur (Guo, 2009; Vercellini et al., 2014). According to a recent meta-analysis, the rates of recurrence at 2 and 5 years after surgery are 20% and 40–50%, respectively (Guo, 2009). Not surprisingly, some authors thus advocate fertility preservation in affected women (Eliur et al., 2009; Donnez et al., 2012; Bedoschi et al., 2013; García-Velasco et al., 2013). On the other hand, it is noteworthy that endometriosis is a common condition, affecting 5–10% of reproductive age women (Viganò et al., 2004) and including all patients with a diagnosis of endometriosis in a fertility preservation program would have profound clinical, logistic and financial effects. A preliminary in depth analysis of the evidence is imperative prior to implementing such a policy.

Hence, our intention here is to outline and evaluate the pros and cons of fertility preservation in women with endometriosis and to speculate on which subgroups of women may benefit from the procedure.

Methods

We searched PubMed for articles published in the English language between January 2000 and January 2015 using the following MeSH search terms: ‘endometrioma’ OR ‘endometriotic’ OR ‘endometriosis’ combined with ‘fertility preservation’ OR ‘oocyte cryopreservation’ OR ‘ovarian cortex’. Data on endometriosis-related damage to the ovarian reserve, oocyte freezing and fertility preservation were obtained by consulting most recent reviews on this argument and completed with specific Pubmed searches for original articles over the last 5 years. Manual search of cross references completed the search. Data presented exclusively as abstracts in national and international meetings were excluded.

Endometriosis, infertility and ovarian reserve: a complex interaction

Endometriosis is detected in 30–50% of infertile women (Viganò et al., 2004) and about half of women with a surgical diagnosis of the disease subsequently fail to achieve natural pregnancy (Somigliana et al., 2009; Adamson and Pasta, 2010; Adamson, 2013; Tomassetti et al., 2013). Overall, even if accurately predicting infertility remains challenging in women with endometriosis (Adamson, 2013), a relationship between the two is indisputable (de Ziegler et al., 2010; Vercellini et al., 2014) and it can be reasonably inferred that up to 50% of affected women may require IVF.

The impact of endometriosis on ovarian reserve is more controversial. The vast majority of the available evidence shows that the classical laparoscopic stripping of ovarian endometriomas damages the ovarian reserve. Even if a recent meta-analysis did not show any modification of the antral follicle count (AFC) after surgery (Muzzi et al., 2014), the remaining evidence strongly supports a relevant injury. Serum AMH decreased significantly after surgery (Raffi et al., 2012; Somigliana et al., 2012), ovarian function test results were severely compromised in 10–15% of the operated gonads (Busacca et al., 2006; Benaglia et al., 2010), ovarian response to hyper-stimulation for IVF treatments was halved (Somigliana et al., 2011). Moreover, women operated on for bilateral endometriomas entered menopause earlier (Coccia et al., 2011) and had a low but consistent risk of post-surgical ovarian failure (Busacca et al., 2006; Di Prospero and Micucci, 2009). Alternative surgical techniques, such as the use of a laparotomic rather than a laparoscopic approach, the use of surgical suture rather than electrocoagulation to achieve haemostasis, the drainage and laser-vaporization of the cyst wall without stripping or a combination of stripping and laser-vaporization, may be less detrimental, but evidence is still weak (Donnez et al., 2010; Coric et al., 2011; Var et al., 2011; Ferrero et al., 2012; Zaitoun et al., 2013; Song et al., 2014).

A point of controversy is the impact of endometriosis per se on ovarian reserve, i.e. independently of surgery. Ovarian endometriomas are of particular concern here since these cysts contain a plethora of potentially toxic agents such as free iron that may diffuse through the cyst wall and damage the ovarian reserve (Sanchez et al., 2014). Moreover, the ovarian cortex of affected gonads is exposed to the potentially detrimental effects of a mechanical long-lasting stretching effect consequent to the presence of the cysts (Sanchez et al., 2014). Recent histological insights showed a significant reduction of the pool of primordial follicles in the ovarian cortex of affected gonads (Kitajima et al., 2011, 2014). One may thus reasonably infer a detrimental effect of ovarian endometriomas prior to their surgical removal. However, the consistent amount of biological evidence suggesting a harmful effect contrasts with the few and inconsistent clinical data. In women with unilateral endometriomas, ovulation occurs less frequently in the affected ovary (Horikawa et al., 2008; Benaglia et al., 2009) but ovarian responsiveness to hyper-stimulation and oocyte competence is similar (Almog et al., 2011; Benaglia et al., 2011; Esinler et al., 2012; Ashrafi et al., 2014; Coccia et al., 2014; Filippi et al., 2014). Serum AMH is unaffected in women with unilateral disease but reduced in those with bilateral lesions (Somigliana et al., 2014). Fewer oocytes are retrieved from women with bilateral endometriomas undergoing IVF but their chances of pregnancy are unaffected (Reinblatt et al., 2011; Benaglia et al., 2013). We believe that the dimension of the endometriomas has a role in explaining the conflicts in the data. It is noteworthy that most of the evidence in unoperated gonads was obtained from women with small endometriomas and extrapolation from data obtained in women with small endometriomas to the whole population of affected patients is at least arguable. Overall, based on the available contributions, it seems reasonable to conclude that ovarian endometriomas may affect ovarian reserve and surgery may significantly worsen this damage.

Fertility preservation in women with endometriosis: state of the art

In contrast to the large body of evidence supporting the validity of the vitrification procedures for oocytes freezing for donation (Cobo and Diaz, 2011; Cil et al., 2013; Potdar et al., 2014), clinical data on the quality of oocytes specifically banked for fertility preservation purposes are still scanty. Even if there is no reason to think that the rate of success would differ markedly between women who donate their oocytes and those banking their eggs for fertility preservation, robust data are required to verify this assumption. Women banking oocytes for medical indication may indeed partly differ. For instance, ovarian responsiveness to hyper-stimulation was shown to be reduced in women with malignancies (Friedler et al., 2012). Moreover, data on the quality of vitrified oocytes in this group of women are very scanty since, to date, only eight live births were reported (Alvarez et al., 2014; Martinez et al., 2014).
Considering specifically endometriosis, the first case of egg banking for fertility preservation in an affected woman was reported by Elizur et al. (2009). These authors froze 21 oocytes that were retrieved following three hyper-stimulation cycles. The woman was 25 years old and previously underwent four interventions for endometriosis (in one of them she had unilateral oophorectomy). Oocytes were not thawed and data on the chances of pregnancy are thus unavailable (Elizur et al., 2009). Garcia-Velasco et al. (2013) recently reported on 5 years of experience with oocyte vitrification. Fertility preservation for endometriosis was performed in 38 women, of whom 5 have already thawed their oocytes. Unfortunately, the precise characteristics of included women and the outcome of the five thawed cases were not reported in details (Garcia-Velasco et al., 2013).

Although scanty, there is some evidence also on endometriosis as an indication for ovarian cortex freezing. In 2005, Donnez et al. firstly provided evidence that this approach might work. They transplanted in two women cortical strips obtained from an ovary carrying a large endometrioma beneath the contralateral ovarian hilus and documented macroscopically viable-looking ovarian tissue in the site of transplant at second-look laparoscopy (Donnez et al., 2005). Finally, Oktay and Oktem (2010) reported a single case of a woman who underwent ovarian cryopreservation at 28 years of age and who subsequently had the ovarian fragments transplanted into the left pelvic peritoneum 1 year later when she was in menopause. At her last follow-up 9 months after the intervention, the woman had normal ovulatory cycles.

Overall, clinical data on egg and ovarian cortex freezing in women with endometriosis are very scanty. On this basis, advocating systematic fertility preservation is utterly premature. It is worth remembering here that, as alluded to above, these points to be kept in mind are summarized in Table I. Some of them have already been mentioned and others are well-known. Discussing in details all the points is beyond the scope of the present review. However, two aspects deserve some justification here.

Firstly, second-line surgery for endometriosis is poorly effective in relieving infertility (Vercellini et al., 2009a,b). The adjusted incidence rate ratio (IRR) of natural conception after second surgery in women who did and did not seek pregnancy before the second intervention was 0.55 (95% CI: 0.30–0.99) and 0.51 (95% CI: 0.32–0.82), respectively (Vercellini et al., 2009b).

Secondly, recent evidence clearly shows that oral contraceptives (OC) markedly prevent recurrence of ovarian endometriomas. This is in accordance with the growing evidence suggesting a crucial role of ovulatory events in the pathogenesis of these cysts (Vercellini et al., 2010). According to a recent meta-analysis, the odds ratio (OR) of endometrioma recurrences in OC users compared with never users is 0.12 (95% CI: 0.05–0.29) (Vercellini et al., 2013). This aspect is of utmost relevance here considering that, as alluded to above, these cysts and their surgical removal are particularly involved in the endometriosis-related damage to the ovarian reserve. In fact, ovarian endometrioma recurrences can be effectively prevented in a simple and economic way.

### Table 1 Assumptions used for the evaluations on the potential relevance of egg banking in women with endometriosis.

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>Level of evidence</th>
<th>Main publicationsa</th>
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<tbody>
<tr>
<td>Assumptions for endometriosis</td>
<td></td>
<td></td>
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<tr>
<td>Endometriosis affects fertility</td>
<td>++</td>
<td>de Ziegler et al. (2010) and Adamson (2013)</td>
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<tr>
<td>Endometriosis is a recurrent disease</td>
<td>++</td>
<td>Guo (2009)</td>
</tr>
<tr>
<td>Ovarian surgery markedly damages ovarian reserve</td>
<td>++</td>
<td>Somigliana et al. (2011) and Raffi et al. (2012)</td>
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<tr>
<td>Ovarian endometriomas damage ovarian reserve</td>
<td>+</td>
<td>Sanchez et al. (2014), Ashrafi et al. (2014), Filippi et al. (2014) and Coccia et al. (2014)</td>
</tr>
<tr>
<td>Second surgery for endometriosis is poorly effective on infertility</td>
<td>++</td>
<td>Vercellini et al. (2009a,b)</td>
</tr>
<tr>
<td>Estroprogestins prevent endometrioma formation</td>
<td>+++</td>
<td>Vercellini et al. (2010, 2013)</td>
</tr>
<tr>
<td>Assumptions for oocyte preservation</td>
<td></td>
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<tr>
<td>Oocytes preservation success depends on age</td>
<td>+++</td>
<td>Stoop et al. (2014)</td>
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<tr>
<td>Oocytes preservation success depends on ovarian reserve</td>
<td>+ +</td>
<td>La Marca and Sunkara (2014)</td>
</tr>
<tr>
<td>Ovarian reserve declines with age</td>
<td>+ +</td>
<td>Nelson et al. (2013)</td>
</tr>
<tr>
<td>The prognosis of IVF is not affected by previous adnexectomy</td>
<td>+ +</td>
<td>Khan et al. (2014)</td>
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<tr>
<td>More than one cycle of hyper-stimulation can be done</td>
<td>+ +</td>
<td>Elizur et al. (2009)</td>
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Level of evidence is judged in a semi-quantitative manner based on the literature and commonsense.

*aIf available, systematic reviews and meta-analyses are cited. Otherwise, the most relevant publications are included.
In order to sort out all the intricate points summarized in Table I into straightforward practical considerations, we analyze separately different clinical scenarios. Results from these evaluations are summarized in Table II. In the table, the different conditions are reported in decreasing order of the potential benefits of fertility preservation. We speculate that fertility preservation may be particularly indicated for women facing a consistent risk of bilateral ovarian damage (i.e. women with bilateral endometriomas and those operated unilaterally with a contralateral recurrence).

The role of the woman's age deserves independent attention. Women with a diagnosis of endometriosis at a young age may have a greater risk of recurrence. Endometriomas and those operated unilaterally with a contralateral recurrence (Table II). Young age at diagnosis may be an independent but pivotal additional factor to be taken into consideration in the balance of the pros and cons of the procedure. Furthermore, the evaluation should be comprehensive and should also take into consideration other factors such as a familial history of premature ovarian insufficiency, BMI, alcohol, smoking and biomarkers of ovarian reserve (Hvidman et al., 2015). Considering the possible therapeutic options, egg banking should currently be preferred to ovarian cortex freezing because of the more solid available evidence (Practice Committee of American Society for Reproductive Medicine, 2013). The latter option should however be considered as an alternative possibility, particularly when radical surgery is envisaged.

However, pilot studies aimed at assessing the feasibility and potential benefits of fertility preservation procedures in women with endometriosis are imperative prior to their introduction in routine clinical practice. This admonition is based on three main reasons.

Firstly, all the considerations included in the present paper are speculative, as concrete data cannot be provided. Although the reasoning is based on robust assumptions (Table I), data on women with endometriosis who actually underwent fertility preservation are extremely limited. Of relevance here is that we lack precise estimates of the consequences of many of the assumptions. For instance, the inference that half of women will be infertile and thus would benefit from egg freezing may be an undue over-estimation since most could achieve pregnancy with fresh IVF. Overall, inaccurate estimates may significantly affect the conclusions, in particular in terms of cost-utility. Noteworthy, economic analyses are mandatory prior to implementing any new approach in modern medicine. In this regard, it is also noteworthy that the few available cost-utility analyses on fertility preservation for age-related fertility decline lead to inconsistent results (van Loendersloot et al., 2011; Hirshfeld-Cytron et al., 2012). Clarifying this point may also provide valuable information for the specific context of fertility preservation in women with endometriosis. Indeed, if future cost-utility analyses will definitely demonstrate a benefit for ageing women, the debate on endometriosis would become obsolete. If fertility preservation would be of value for all women, it would be highly likely to be even more valuable for women with endometriosis.

Secondly, endometriosis is a relatively common condition. It has an estimated prevalence of 5–10%, corresponding to about 176 million women being affected worldwide (Nnoaham et al., 2011). Sustainability is an important concern here. A widespread diffusion of fertility preservation in women with endometriosis would have a dramatic impact on the public health systems and there is a consistent risk of inappropriate allocation of healthcare resources. Thus, fertility preservation for endometriosis cannot (must not) be proposed without robust evidence. Preliminary pilot programs in referral centers are warranted.

### Conclusions

Fertility preservation may be of interest for women with endometriosis, in particular in women with bilateral unoperated endometriomas and in those who previously had excision of unilateral endometriomas and require surgery for a contralateral recurrence (Table II). Young age at diagnosis may be an independent but pivotal additional factor to be taken into consideration in the balance of the pros and cons of the procedure. Furthermore, the evaluation should be comprehensive and should also take into consideration other factors such as a familial history of premature ovarian insufficiency, BMI, alcohol, smoking and biomarkers of ovarian reserve (Hvidman et al., 2015). Considering the possible therapeutic options, egg banking should currently be preferred to ovarian cortex freezing because of the more solid available evidence (Practice Committee of American Society for Reproductive Medicine, 2013). The latter option should however be considered as an alternative possibility, particularly when radical surgery is envisaged.
Thirdly, the introduction of systematic fertility preservation in the management of women with endometriosis may have some secondary unpredictable negative effects. Women may take the success of egg freezing for granted and may unwisely delay childbearing. Even if a recent follow-up of women who have banked oocytes for the prevention of age-related fertility decline does not support this concern (Stoop et al., 2015), it has to be pointed out that specific data in women with endometriosis are lacking and we cannot exclude that this detrimental effect may actually occur in this population. It is noteworthy that even though endometriosis may affect IVF success, it is considered a valid indication for the effective options already available. Of utmost relevance here, fertility preservation procedures. A second potential harmful drawback of fertility preservation is that physicians and patients may give less importance to the effective options already available. Of utmost relevance here, is the previously mentioned outstanding capacity of OCs to prevent formation of ovarian endometriomas (Vercellini et al., 2013). This is a crucial point since surgery for endometriomas may compromise ovarian reserve and ovarian reserve is critical for IVF success. Again, we can speculate that fertility preservation without OCs may ultimately be less effective than long-term OCs without fertility preservation. It is noteworthy that there is no evidence that delaying seeking pregnancy after surgery may markedly affect the chances of natural pregnancy, provided that a recurrence did not develop in the meantime (Somigliana et al., 2010).

On the other hand, a possible concern here is that the long-term OC use may mask ovarian reserve as patients are unaware of anovulation. In conclusion, endometriosis might be an indication for fertility preservation. However, robust clinical data and cost-utility analyses are warranted prior to implementing its use in routine clinical practice.

Authors’ roles

E.S., P.V. and F.F. conceived and designed the study. All the authors participated to several investigational meetings aimed at drawing clear recommendations for fertility preservation in the two referring Institutions (Fondazione Ca’ Granda and San Raffaele Scientific hospital). E.S. and P.V. drafted the first version of the manuscript. All the other authors revised the manuscript.

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Conflict of interest

None declared.

References

Brosens I, Gordo S, Benagiano G. Endometriosis in adolescents is a hidden, progressive and severe disease that deserves attention, not just compassion. Hum Reprod 2013;28:2026 –2031.

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