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Opinion

Fertility preservation in women with benign gynaecological conditions

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ABSTRACT

Although a wealth of data has been published regarding fertility preservation (FP) in women with malignant diseases who receive gonadotoxic treatment, the role of FP in non-malignant conditions has been studied to a much lesser extent. These include benign haematological, autoimmune, and genetic disorders, as well as a multitude of benign gynaecological conditions (BGCs) that may compromise ovarian reserve and/or reproductive potential due to pathogenic mechanisms or as a result of medical or surgical treatments. Alongside accumulating data that document the reproductive potential of cryopreserved oocytes and ovarian tissue, there is potential interest in FP for women with BGCs at risk of infertility; however, there are currently insufficient data about FP in women with BGCs to develop guidelines for clinical practice. The purpose of this article is to appraise the available evidence regarding FP for BGC and discuss potential strategies for FP based on estimated ovarian impairment and on short-term and long-term reproductive goals of patients. Cost-effectiveness considerations and patients' perspectives will also be discussed.

Keywords: adenomyosis, endometriosis, cryopreservation, female infertility, fertility preservation, oocyte quality, ovarian reserve, ovary, premature ovarian insufficiency

Introduction

During the last decade, technological advances and increased experience with oocyte vitrification and ovarian tissue cryopreservation for subsequent autografting have allowed the development of effective female fertility preservation (FP) (Cao *et al.*, 2009; Donnez and Dolmans, 2017; Rienzi *et al.*, 2017). Initially used for women requiring gonadotoxic chemotherapy and/or radiotherapy, indications for FP have recently extended to non-malignant conditions and associated treatments that might also lead to follicular loss, including immunological, haematological, or genetic pathologies, as well as age-related fertility decline (Donnez and Dolmans, 2017; Cobo *et al.*, 2018; Loren and Senapati, 2019; Anderson *et al.*, 2020).

Although less frequently reported, numerous benign gynaecological conditions (BGCs) that can result in premature ovarian insufficiency (POI) and/or lead to infertility are also potential indications for FP (Somigliana *et al.*, 2015; Condorelli and Demeestere, 2019). In some situations, ovarian reserve and future fertility can be compromised: owing to the disease itself, as in patients with endometriosis; because of delayed pregnancy, as can occur when multiple and large leiomyomas need to be removed surgically before pregnancy is attempted; or when surgical treatment is likely to destroy healthy ovarian tissue, as for presumed bilateral or recurrent benign ovarian tumours.

Although BGCs may be associated with impaired fertility, healthcare providers do not often discuss the option of FP with patients who may be at risk of infertility due to BGCs. This observation is based on the low number of studies on FP for BGCs compared to those on FP for malignant disease (Anderson *et al.*, 2020). Our objective is to appraise the available evidence and discuss potential scenarios where use of FP might be beneficial in BGCs, to help practitioners to make appropriate patient assessments and choices for FP interventions. This might enable some women with BGCs to create supplementary options for future parenthood using autologous oocytes. We present potential indications for FP in these scenarios (Fig. 1), review obstetric and neonatal outcomes, and discuss the patient's perspective, as well as cost–benefit considerations, on the basis of available scientific evidence.

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Indications for fertility preservation in BGCs

Fertility preservation in women with low ovarian reserve

Diagnosis of low ovarian reserve is usually based on elevated basal FSH levels, low anti-Müllerian hormone (AMH) levels, and low antral follicle count, among women who are still having periods (Practice Committee of the American Society for Reproductive Medicine, 2020).

Although low ovarian reserve is most commonly a physiological consequence of age, several conditions can affect the ovaries and cause accelerated decline in primordial follicle number (Wang *et al.*, 2014; Phillips *et al.*, 2016; Pastore *et al.*, 2018). Referral for FP counselling may be appropriate as soon as such a condition is diagnosed, rather than waiting for a deterioration of ovarian reserve (Vergier *et al.*, 2019; Ulrich *et al.*, 2022). Indeed, there is a window of opportunity for diagnosing impending POI in its early course, before reduced ovarian reserve has progressed to POI and while FP is still feasible. However, no robust data regarding the long-term safety and efficacy of FP in women with POI are available to date.

The distinction between a physiological and a pathological decline in ovarian reserve may not be straightforward. Although nomograms have been developed for serum AMH levels throughout the reproductive lifespan, it is important to understand that the decision to start FP might not be based on a single assessment indicating low ovarian reserve, as it cannot distinguish between a constitutionally low number of follicles, which does not impact fecundability in natural conception (Hagen *et al.*, 2012; Zarek *et al.*, 2015), and a pathologically accelerated decline of primordial follicle number, ultimately resulting in POI. Moreover, low AMH levels in young women must be interpreted with caution as AMH levels typically increase during adolescence and plateau between 20 and 25 years of age (Dewailly *et al.*, 2014). In those situations, the decision to stimulate the ovaries for oocyte cryopreservation might be considered less urgent. Instead, given the lack of scientific evidence, longitudinal monitoring of serum AMH levels could be proposed to identify accelerated follicle loss among young women with constitutionally low ovarian reserve or a family history of POI, and oocyte cryopreservation for FP advocated when AMH levels decrease at a non-physiological rate over consecutive time points.

While there are few data regarding success rates of oocyte cryopreservation in women with impending POI, a model based on elective FP data in women with uncompromised ovarian reserve provides some evidence that even a small number of cryopreserved oocytes can predict a reasonable chance of a live birth; in this model, as few as five vitrified oocytes in a woman aged 25–30 years would confer a 44% probability of at least one live birth (Goldman *et al.*, 2017). It could be surmised that similar outcomes might be achieved in young women with low ovarian reserve. Although oocyte yield per cycle in young poor responders might be low (Oktay and Bedoschi, 2014; Ulrich *et al.*, 2022), and the number of vitrified oocytes correlates with pregnancy outcome whatever the FP indication (Cobo *et al.*, 2021), pooling of oocytes collected over several cycles could be a realistic option for women with impending POI (Ito *et al.*, 2020). However, the risks of FP in these patients have not been clearly assessed and the psychological impact of these procedures should not be underestimated. Counselling and psychological support are recommended when dealing with FP decisions (Anderson *et al.*, 2020), as the extent of the clinical benefit has not been studied. Finally, it is important to inform patients that alternatives to FP exist, including oocyte donation, embryo donation, and adoption; and child-free living may be a reasonable choice for some women (Baker, 2011).

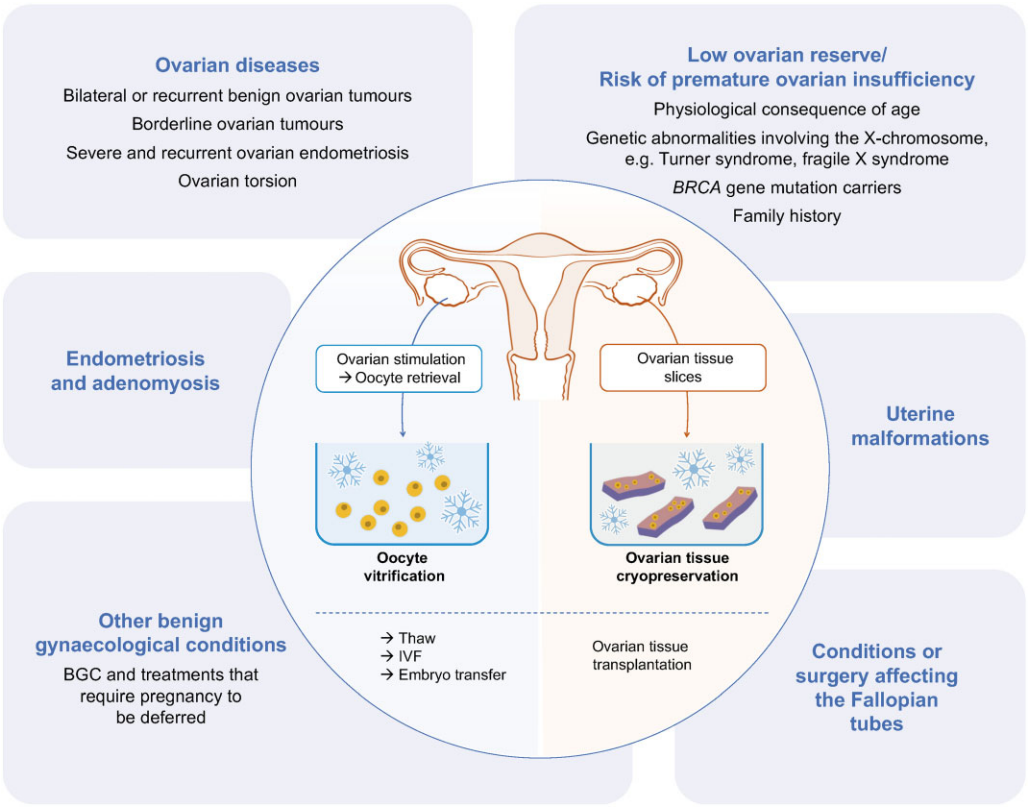

Figure 1. Indications where fertility preservation should be discussed in women with benign gynaecological conditions, and the options available.
BGC, benign gynaecological condition; *BRCA*, breast cancer gene.

Irrespective of whether young women with low serum AMH levels decide to embark on FP, there is a need for public awareness campaigns to assist women in understanding the consequences of age-related fertility decline (Hvidman et al., 2015; Pedro et al., 2018). The role of ovarian reserve testing, to identify women at increased risk of POI, and the value of FP in these women should also be the focus of future research.

Fertility preservation in young women with genetic conditions associated with POI

Around 10% of cases of POI are a result of genetic conditions, including Turner syndrome, fragile X pre-mutation, and a large number of rare genetic syndromes (De Vos et al., 2010; La Marca and Mastellari, 2021). Where a genetic anomaly carrying a potential risk of decreased ovarian reserve is identified, patients should receive specific FP counselling to be informed about their reproductive status, including information on the risk of transmission, and to discuss options and plan for FP, including the possibility of preimplantation genetic testing. Turner syndrome is one of the most common genetic conditions associated with low ovarian reserve and in most cases results in POI before adulthood (Hreinsson et al., 2002). In adolescents and young women with 45,X/46,XX mosaicism (about 20–30% of individuals with Turner syndrome), menarche is more frequent and menstrual cycles are likely to continue for longer than in women with full-blown 45,X karyotype. FP may be feasible in this case and, if selected, should be undertaken before the onset of secondary amenorrhoea, as soon as the diagnosis is made and providing the (adolescent) patient is mature enough and emotionally able to undergo ovarian stimulation (OS) (Oktay and Bedoschi, 2014).

Thus, in young individuals with a genetic disease leading to POI, assessment, and selection for FP interventions can be rather complex. The choice of the most suitable technique, the optimal age for intervention before the onset of POI, the health implications of a possible future pregnancy as well as the risk–benefit evaluation should be considered and may require a multidisciplinary approach involving paediatricians, obstetricians, and psychologists (La Marca and Mastellari, 2021).

Ovarian cysts and tumours

Surgical excision of benign ovarian tumours can compromise ovarian reserve, with a more pronounced impact in bilateral or recurrent tumours (Donnez and Dolmans, 2017). FP has been proposed for several indications in this context: bilateral ovarian cystectomy, recurrent adnexal torsion, unilateral adnexectomy, and suspected malignancy or necrosis secondary to protracted torsion resulting in the presence of a single residual ovary (Sleiman et al., 2019; Legrand et al., 2021). In view of the lack of generalized recommendations, a personalized approach is necessary.

Borderline ovarian tumours

Borderline ovarian tumours (BOT), or low malignant potential ovarian epithelial tumours, are a group of ovarian neoplasms described as 'semi-malignant disease' (Maramai et al., 2020) and constitute a specific and controversial indication for FP. A surgical approach is advocated, the extent of which depends on the disease stage (Minig et al., 2016; Casarin et al., 2020). Overall survival for patients undergoing fertility-sparing surgery, encompassing the removal of neoplastic tissue whilst preserving the uterus and at least part of one ovary, is close to 100% (Morice et al., 2001; Zanetta et al., 2001; Mandelbaum et al., 2019). However, for mucinous BOT, cystectomy is not recommended because of the high risk of recurrence and progression to carcinoma (up to 13% at 10 years versus 2% at 10 years for serous BOT associated with invasive implants) (Koskas et al., 2011).

Given the low incidence of around 1.5–4.8 new cases per 100 000 women per year (Lalwani et al., 2010; Tropé et al., 2012), there is little published experience regarding FP in women with BOT, and recurrence rates of BOT after surgical excision are relatively high. Nevertheless, FP using OS and oocyte vitrification is a suitable option for younger women, in whom these tumours tend to be more prevalent, and for those with bilateral BOT or previous history of unilateral adnexectomy. FP should be scheduled after surgical excision of the tumour to avoid spillage of neoplastic cells during transvaginal oocyte retrieval (Mangili et al., 2016).

There are no published data relating to the impact of ovarian surgery for BOT on AMH levels. In a series of 17 women selected for IVF or ICSI who had previously undergone unilateral laparoscopic excision of benign non-endometriotic ovarian cysts, OS resulted in significantly reduced numbers of dominant follicles in the previously operated ovary compared with the healthy ovary (Somigliana et al., 2006). A large retrospective population-based survey showed that women who had undergone unilateral oophorectomy experienced menopause around 1 year earlier than women with two ovaries. However, this effect was smaller than anticipated, suggesting that the remaining ovary might compensate for the reduction in ovarian reserve (Bjelland et al., 2014). Other evidence suggests some recovery of ovarian reserve following ovarian surgery for BOT: a prospective, longitudinal study of women undergoing laparoscopic cystectomy for benign ovarian masses showed an increase in AMH levels after surgery with no significant difference after 3 months compared with preoperative levels (Chang et al., 2010).

Infertility is reported in approximately 10–35% of patients with BOT (Mangili et al., 2016), but caution is needed with regard to OS for oocyte cryopreservation. Epidemiological studies have shown an increased risk of BOT in women receiving infertility drugs (van Leeuwen et al., 2011; Stewart et al., 2013) and, although there is insufficient evidence of a causal relationship (Mangili et al., 2016), a detrimental effect of OS on BOT growth is plausible. Therefore, OS should not be offered prior to surgery or when BOT is present (Buonomo and Peccatori, 2020). Conversely, some women with a history of BOT have undergone OS without recurrence, with several studies proposing a wait of at least 1–2 years after surgery before attempting ART (Daraï et al., 2013). Concomitant use of letrozole during OS to mitigate the risk of BOT recurrence has been suggested (Mangili et al., 2016), although direct evidence is lacking regarding any effect of oestrogens on ovarian tumour growth.

Ovarian tissue cryopreservation is another option for FP in women with BOT. However, given the potential risk of re-implanting BOT cells when performing a re-implantation of the fragment, this technique should be reserved only for women who would not have ovarian conservation at the time of surgery (i.e. bilateral oophorectomy) (Masciangelo et al., 2018). *In vitro* maturation of immature oocytes retrieved from the visible antral follicles of an ovarian specimen immediately after surgical removal is another potential FP strategy (Donnez and Dolmans, 2017), although this is still considered experimental.

Insufficient attention is given in the literature to the evaluation of fertility potential prior to an intervention for BOT. Patients diagnosed with BOT should be referred to an oncofertility centre prior to surgery to assess their reproductive status and plan operative management (Mangili et al., 2016; Del Pup et al., 2018). The majority of pregnancies reported after conservative management of BOT are in fact natural (Daraï et al., 2013), so the patient should

be encouraged to try for a natural pregnancy if possible to avoid the need for OS and its potential risks (Khiat *et al.*, 2020).

Endometriosis and adenomyosis

Endometriosis

The association between endometriosis and infertility is well established, both clinically and mechanistically (de Ziegler *et al.*, 2010). Endometriosis impacts infertility primarily on reproductive ovarian function and appears to increase the risk of altered ovarian reserve, irrespective of any surgery (Lemos *et al.*, 2008; Sanchez *et al.*, 2014; Hamdan *et al.*, 2015). Recent studies have reported reduced ovarian reserve associated with endometriosis as a result of excessive activation of primordial follicles driven by the PI3K-PTEN-Akt (phosphatidylinositol 3-kinase–phosphatase and tensin homolog–protein kinase B) pathway or inflammatory processes (Kasapoglu *et al.*, 2018; Takeuchi *et al.*, 2019). Nevertheless, a wealth of data indicates that surgery for ovarian endometriosis further impairs ovarian function, with several consequences: risk of premature ovarian failure immediately after surgery (Busacca *et al.*, 2006); risk of early-onset menopause (Coccia *et al.*, 2011); decreased ovarian reserve, highlighted by profound reductions in serum AMH and antral follicular count after surgery (Raffi *et al.*, 2012; Streuli *et al.*, 2012; Hamdan *et al.*, 2015); and decreased ovarian response to stimulation in women undergoing IVF or ICSI (Bourdon *et al.*, 2018; Garcia-Fernandez and García-Velasco, 2020). Reduced ovarian reserve after surgical treatment has been reported even when carried out by expert surgeons (Biacchiardi *et al.*, 2011) and especially in the case of bilateral ovarian lesions (Younis *et al.*, 2019) and iterative surgery (Ferrero *et al.*, 2015; Muzii *et al.*, 2015). Other endometriosis-related factors contributing to infertility include abnormalities of the eutopic endometrium, pelvic adhesions leading to tubal dysfunction, decreased frequency of sexual intercourse owing to pain during sex, and for some patients, the need for continuous antigonadotrophic therapy to relieve painful symptoms (Chapron *et al.*, 2019).

Half of all women affected with endometriosis will experience infertility and may require ART to achieve a live birth (Somigliana *et al.*, 2015). In this setting, ovarian reserve is considered to be one of the main prognostic factors (Maignien *et al.*, 2017; Younis *et al.*, 2019), thus highlighting a need to protect the ovarian follicle pool (Somigliana *et al.*, 2015; Chapron *et al.*, 2019) and supporting an indication for FP in these women.

Although several FP techniques have been proposed, oocyte vitrification is currently considered the safest and most efficient option in women with endometriosis (Somigliana *et al.*, 2015; Cobo *et al.*, 2020; Santulli *et al.*, 2021). Moreover, ovarian response may be more favourable when OS is performed in women without previous history of surgery for ovarian endometriosis (Cobo *et al.*, 2020; Santulli *et al.*, 2021). Thus, FP may be particularly indicated where there is a risk of ovarian damage, notably before surgery. However, the clinical heterogeneity of endometriosis makes decisions around fertility complex. Data concerning the use of vitrified oocytes and live birth chances require further evaluation, and there is a lack of consensus on optimum practice for FP. Questions remain about whether all women affected with endometriosis would benefit from FP and at what stage FP should be integrated into endometriosis management (Somigliana *et al.*, 2015). Further investigation is needed to identify those women with endometriosis that have a high risk of being infertile in the future. Thus, it would be premature to recommend routine oocyte banking for women with endometriosis based on evidence to date. Endometriosis is a relatively common disease, and more robust evidence of the value of FP strategies for affected individuals is needed. In addition to the high cost of oocyte banking, FP treatments may expose some women to undue clinical risks. Personalized FP counselling for women with endometriosis is therefore warranted. Finally, if surgical treatment for endometriosis is indicated, fertility-sparing operative techniques that minimize any impact on the ovarian reserve are to be favoured wherever possible. Thus, endometriosis is ideally managed at multidisciplinary expert centres, where all diagnostic and therapeutic possibilities can be offered (Chapron *et al.*, 2019).

Adenomyosis

Adenomyosis, defined as the presence of ectopic endometrial islets within the myometrium (Bergeron *et al.*, 2006), is frequently associated with endometriosis and can cause pelvic pain, abnormal uterine bleeding, and impaired fertility (Vercellini *et al.*, 2014).

Although adenomyosis is not a conventional indication for FP, numerous studies have suggested that this condition could be associated with disorders of fertility among younger women (Kunz *et al.*, 2005; Kissler *et al.*, 2006; Campo *et al.*, 2012; Bourdon *et al.*, 2020b). The mechanisms involved in adenomyosis-related infertility are unclear and do not appear to be associated with decreased ovarian reserve. Nevertheless, it seems that a large proportion of adenomyosis-infertile women would benefit from ART treatment (Vercellini *et al.*, 2014; Younes and Tulandi, 2017). Satisfactory birth rates have been described (Mavrelos *et al.*, 2017; Bourdon *et al.*, 2022) and specific protocols developed to improve the chances of implantation in these patients, notably with the use of a GnRH agonist before embryo transfer (Niu *et al.*, 2013; Vercellini *et al.*, 2014; Rocha *et al.*, 2018). Some teams also proposed conservative surgical techniques, such as adenomyomectomy, although the majority of pregnancies described following surgical treatment were obtained after IVF/ICSI (Rocha *et al.*, 2018). The available medical treatments for adenomyosis-related symptoms include antigonadotrophic drugs, which prevent spontaneous fertility by blocking the hypothalamic–pituitary axis (Vannuccini *et al.*, 2018). For some patients with disabling symptoms, these drugs cannot be discontinued and an IVF/ICSI strategy is the only possibility for having a child.

Taken together, these factors suggest that for some women affected with important/symptomatic lesions of adenomyosis, FP with oocyte freezing could be warranted on a case-by-case basis at a young age, to improve the chances of bearing a child later in life. These women should also be encouraged to have their children before age becomes a limiting factor for successful IVF treatment.

Other benign gynaecological conditions

It is difficult to establish an exhaustive list of BGCs that could compromise ovarian reserve and/or reproductive potential. Besides those described, other BGCs or their treatments could delay time to pregnancy, even if they have no direct negative impact on ovarian reserve. Advice may vary, but following surgery for some BGCs (e.g. resection of multiple and large leiomyomas by laparotomy) the practitioner might recommend deferring pregnancy attempts to limit obstetric complications such as uterine rupture (Dolmans *et al.*, 2021). However, where there is pre-existing decline of ovarian reserve, or beyond a certain age, deferral of pregnancy could decrease the chance of a successful reproductive outcome.

There are also situations where natural conception will not be possible, such as after bilateral salpingectomy or in the case of

uterine malformation (e.g. Mayer–Rokitansky–Küster–Hauser syndrome), and medically assisted reproduction (i.e. IVF, uterine graft or surrogate motherhood) will provide the only opportunity for having biological offspring. In these situations, FP should be discussed as soon as possible to preserve oocytes early in reproductive life for use later when the patient has a desire to become pregnant and to optimize fertility outcomes.

Risk of fertility loss in women with BGCs

Although some indications will result in irreversible fertility loss [e.g. prophylactic bilateral oophorectomy in women with a genetic predisposition to ovarian cancer (Andrews and Mutch, 2017) or a radical surgical intervention in the case of some bilateral ovarian tumours], assessment of the risk of infertility or subfertility posed by each BGC, or its treatment is difficult as it is for some malignant conditions (Condorelli and Demeestere, 2019).

Even when a so-called 'fertility-sparing' ovarian surgery is performed, a reduction of the ovarian follicular reserve will be inevitable, although this reduction may vary (Jia *et al.*, 2020) and will also depend on the surgical skills of the operator (Busacca *et al.*, 2006; Somigliana *et al.*, 2006; Coccia *et al.*, 2011). Nevertheless, even if AMH decline is observed post-surgery (Streuli *et al.*, 2012), low levels of AMH are not necessarily associated with reduced fertility (Hagen *et al.*, 2012). Low AMH levels are associated with reduced ovarian response to gonadotrophins and hence with lower success rates of IVF treatment (Bourdon *et al.*, 2018), and women with low AMH levels may have an increased risk of early menopause (Depmann *et al.*, 2018; Harris *et al.*, 2023). Other BGCs that do not require ovarian surgery can also induce infertility due to the disease pathology itself (Schwartz *et al.*, 1994; Kunz *et al.*, 2005; Kissler *et al.*, 2006; Lemos *et al.*, 2008; De Vos *et al.*, 2010; Campo *et al.*, 2012; Sanchez *et al.*, 2014; Hamdan *et al.*, 2015; Bourdon *et al.*, 2020b; La Marca and Mastellari, 2021).

In view of this, FP in women with BGCs can be considered as an instrument to create an 'insurance supply' of cryopreserved oocytes in case future attempts of natural conception fail and IVF procedures are required, or when loss of fertility caused by premature menopause arises (Mangili *et al.*, 2016; Legrand *et al.*, 2021). FP is a preventative, not curative, treatment. The strategy should be adapted and personalized for each patient.

Estimation of individual risk of fertility loss, the decision-making process, and selection of an FP strategy will be based on several factors and should be supported by comprehensive, transparent provision of patient information. The most important factors are female age, ovarian reserve parameters, and patient intentions and priorities, which will underpin the medical strategy for BGC management.

Obstetric and neonatal outcomes following utilization of cryopreserved oocytes or ovarian tissue

The first pregnancy and live birth after human oocyte cryopreservation was reported in 1986 and 1987, respectively (Chen, 1986; van Uem *et al.*, 1987), and use of FP has continued to expand rapidly. However, little is known about the obstetric risks and neonatal outcomes of pregnancies following FP. For ovarian tissue cryopreservation, although more than 360 frozen-thawed ovarian tissue transplants have been performed worldwide, information on obstetric and perinatal outcomes have been rarely reported and mostly in women with a previous malignant diagnosis (Andersen *et al.*, 2019). Published data on oocyte cryopreservation programmes relate primarily to oocyte donation, where oocytes originate from young, healthy donors, and recipients are likely to be older and with no BGCs. Reports from oocyte donation programmes using young donors reveal similar clinical pregnancy rates after transfer of embryos created from fresh or vitrified oocytes (Cobo *et al.*, 2008). However, continued monitoring of births is paramount, given concerns about the effect of the vitrification process on oocytes and potential adverse effects on pregnancy and perinatal outcomes (Cobo *et al.*, 2014).

The largest study to date looking at obstetric and perinatal outcomes was a retrospective cohort of 1027 children born from 804 pregnancies after use of vitrified donor oocytes (88%) or own oocytes (12%), and a similar number from fresh oocytes (Cobo *et al.*, 2014). No relevant differences were noted for pregnancy, delivery, and neonatal outcomes from frozen or fresh oocytes or from own versus donor oocytes, after adjustment for relevant confounding factors. A higher frequency of invasive procedures (chorionic villous sampling or amniocentesis) was observed in the vitrified oocytes group (adjusted odds ratio (aOR) 2.12, 95% CI 1.41–3.20), although no abnormal results were found in these tests.

The UK Human Fertilisation and Embryology Authority (HFEA) database (2000–2016) includes data on live birth rates (LBR) and perinatal outcomes after the use of frozen own ($N = 632$) versus frozen donor ($N = 922$) oocytes (Mascarenhas *et al.*, 2021). Singleton LBR and frequency of low birthweight (LBW) were significantly lower with frozen own oocytes than with frozen donor oocytes (LBR 15.0% versus 25.5%, aOR 0.52, 95% CI 0.40–0.67; LBW rate 5.3% versus 14.0%; aOR 0.29, 95% CI 0.13–0.90). There was, however, no significant difference in preterm birth (9.5% versus 15.7%; aOR 0.56, 95% CI 0.26–1.21). Fresh and frozen donor oocytes resulted in similar LBR and perinatal outcomes. Results also supported the 'immune' hypothesis of adverse perinatal outcomes in pregnancies following egg donation (Mascarenhas *et al.*, 2017; Storgaard *et al.*, 2017), which does not seem to occur with own oocytes.

Overall, the limited available data show no apparent increase in birth defects following oocyte vitrification. However, further prospective studies are required to evaluate outcomes following FP in specific scenarios, including social freezing, malignancies, and BGC, as well as use of own or donor oocytes. National IVF registers and fertility centres performing FP should systematically collect data on indications for FP and obstetric and perinatal outcomes.

Fertility preservation from the patient's perspective

The experience of utilizing FP in patients with cancer has highlighted the psychological importance to patients of storing eggs or ovarian tissue for future use (Logan and Anazodo, 2019). Fertility counselling is particularly vital for young women with newly diagnosed cancer before they receive a treatment that could harm their fertility and can be associated with greater quality of life after treatment, whether or not FP is offered (Letourneau *et al.*, 2012). The threat of infertility and the fear of never being able to conceive is a huge burden for many cancer patients, with potential negative effects on identity and psychological well-being (Armuand *et al.*, 2018). Fear of infertility is equally likely to be a concern for patients with BGCs. Indeed, 96% of women with endometriosis who participated in a web-based survey worried about their fertility in relation to their disease, and only 27% considered themselves well-informed by their

doctor (Navarria-Forney *et al.*, 2020). Diagnosis of POI in adolescents has been linked to psychological distress and anxiety, highlighting the importance of involving the family and referring to appropriate counselling resources (Gordon *et al.*, 2015). With a renewed focus over the last couple of decades on the importance of FP counselling for young cancer patients (Dolmans *et al.*, 2019), the question remains as to whether clinicians caring for patients with BGCs are equally good at offering counselling and FP, where appropriate. In a recent French study, 74% of surgeons and reproductive clinicians considered and offered FP strategies to their patients with bilateral or recurrent endometriomas (Jourdain *et al.*, 2021). In general, however, studies on FP in patients with BGCs are scarce. It is unclear how many patients with BGCs are offered FP, and whether lack of awareness among treating clinicians may represent a barrier to accessing FP. Other potential challenges include financial limitations, national legislation, religious and social considerations and, in minors, unwillingness of the parents or legal guardians to allow the adolescent to undergo FP. It is essential to inform patients considering FP about the risks and limitations associated with the treatment and processes involved, including whether statutory storage limits exist, under which terms extension beyond this is permissible, and any other local legislative restrictions, which differ substantially between countries. FP might generate a false sense of security of having an assured future 'reproductive capital', which could delay the patient's active engagement to achieve a pregnancy until advanced maternal age. The probability of future successful reproductive outcomes for the individual/couple and whether there may be restrictions on their treatment based on age or other factors should also be discussed.

Effectiveness and cost-benefit considerations for fertility preservation in BGCs

Research into the true effectiveness of FP interventions in BGCs, in terms of future use of cryopreserved oocytes and rates of successful reproductive outcomes are lacking. Therefore, it is difficult to evaluate the cost-effectiveness of FP for BGCs, and to our knowledge, there are no published data that address this specific scenario. The monetary cost of the procedure is an important issue given that egg banking is expensive (Ben-Rafael, 2018). Additionally, the proportion of women who will return to utilize their oocytes is still rather low, and this is an important driver of cost–benefit. In the context of social freezing, usage rates of frozen eggs are reported to be <10%, equating to an estimated cost per live birth of $600 000–$1 000 000 (Ben-Rafael, 2018). In view of this, applying FP to all women with BGCs, even with limited risk of fertility loss, will result in large numbers of stored but unused reproductive materials, creating an unnecessary burden and costs for some patients involved and for health services. Therefore, a liberal indication for FP in women with BGCs is not recommended (Anderson *et al.*, 2020). In the absence of cost-effectiveness data, one must conclude that a broad indication of FP for benign disorders cannot be advocated on a large scale.

In addition to monetary costs, psychological or physical stress associated with FP treatment present a considerable upfront burden for a future benefit that is not guaranteed. Women requiring FP are predictably younger than the average ART population and, therefore, may be more exposed to financial or emotional constraints. Ethical issues should also be a part of FP counselling and the decision to offer FP or not. Individual considerations are necessary in each case, with reference to each patient's physical, mental, and social circumstances. While most clinicians and patients view FP as a positive intervention, negative perceptions also exist. A recent survey of 42 Danish women who had undergone ovarian tissue cryopreservation for malignant or benign indications found that ovarian tissue cryopreservation represented the future and provided hope for women, but it was also associated with feelings of fear and re-connected the patient with their disease (Bach *et al.*, 2020).

Therefore, the indication must be carefully considered. Practitioners must address the sensitive topic of fertility with patients with BGCs and each potential indication for FP must be evaluated individually. The potential risk of fertility loss due to the disease should be weighed against the risks and benefits of FP, including the likelihood of achieving a future successful birth after use of the preserved material, and the cost of the intervention, as well as considering the alternatives to FP, in order to plan for their future parental goals. Even if the true benefit of FP remains unknown for women with BGCs, patients must be given all the available information to make an informed decision about whether or not to undergo FP, keeping in mind that many of the situations occur at an age at which there is no dilemma since, depending on country legislation, social freezing may also be an option.

Effectiveness of FP interventions in BGCs is difficult to assess. Undoubtedly, cryopreservation suspends the inexorable deterioration of oocytes and embryo quality that accompanies female ageing. FP interventions can allow sufficient time to be taken to treat BGCs, which could affect the establishment of a viable pregnancy. Storage can also prevent exposure of reproductive material to gonadotoxic therapeutics if they are required. Together, these elements can positively influence the effectiveness of FP treatments. However, the degree of overall success also depends on other factors. The quality and quantity of stored oocytes directly influence the chances of a successful clinical outcome in FP. Therefore, the possibility of reduced oocyte quality associated with gynaecological conditions demanding an FP intervention should be thoroughly assessed. In terms of quantity, data from elective FP cycles indicate that, in women younger than 35 years, storage of five oocytes corresponds to a cumulative live birth rate of ~15%, whereas a higher number of cryopreserved oocytes (10–20) assures more robust cumulative probabilities (between 40% and 85%) of achieving a live birth (Cobo *et al.*, 2016). Notably, such rates are more than halved in older women. Evidence from large series about elective FP supports discussions with patients about the chances of pregnancy based on their age and the number of frozen oocytes available (Cobo *et al.*, 2016; Goldman *et al.*, 2017). Among other factors, the clinician should assess ovarian reserve, with particular attention on the age of the candidate for FP, for realistic chances of success after oocyte cryopreservation. Therefore, early decision-making for FP becomes crucial. Accumulation of a suitable number of cryopreserved oocytes is also appropriate. In the absence of any time constraints, it may be advisable to perform several OS cycles, to accumulate a larger number of vitrified mature oocytes and increase the chance of a live birth in the event of their future use (Bourdon *et al.*, 2020a). Nevertheless, when considering FP, it is essential to adopt an individualized approach and to discuss the potential risks, costs and benefits with the patient when deciding on the ideal OS protocol. It is important not to expose women to any undue clinical risks. Table I summarizes several potential concerns regarding an ideal FP procedure and the options to be considered in order to mitigate them. The optimal timing for FP is also a key factor (Fig. 2).

Table I. Concerns to address for an ideal fertility preservation procedure.

	Safety	Optimal response	Convenience
Overall objectives	Prioritize safety for the patient.	Attempt to obtain an optimal response from the ovaries. This is one of the main topics to discuss with patients prior to undergoing FP.	Minimize inconveniences associated with treatment administration and side effects. Avoid unnecessary scans or blood tests, to reduce visits to the hospital.
Issues	OHSS is the most frequent and critical complication from OS (Gómez *et al.*, 2010). In women with a high response to OS, early OHSS can develop after the hCG trigger. Late OHSS can be induced by the hCG produced by the trophoblast. Other complications such as ovarian torsion, infections, or bleeding are infrequent (Bodri *et al.*, 2008).	Key factors that increase the chance of future successful live birth are lower age at which oocytes are cryopreserved (<35 years) and higher number of oocytes (Cobo *et al.*, 2016; Goldman *et al.*, 2017). Most women who consider FP are >35 years of age. Targeting a good number of oocytes must be balanced with avoiding over-aggressive protocols that might cause OHSS.	There may be time constraints. Women undergoing FP for medical reasons may be suffering from diseases that allow them a very limited time frame to collect oocytes for cryopreservation. Women undergoing FP often have busy lives and may be unable or unwilling to dedicate excessive time to intensive or repeated treatment and monitoring protocols.
Mitigation strategies	Avoid excessive OS. The risk of OHSS is lower for FP cycles as they will not need an hCG trigger and will not undergo embryo transfer after the OS cycle (avoiding late OHSS). ESHRE guidelines (Bosch *et al.*, 2020a) recommend GnRH antagonist-based protocols, as they shorten the duration of the treatment and allow the use of a GnRH agonist trigger rather than hCG (Humaidan *et al.*, 2011; Fatemi and Garcia-Velasco, 2015), minimizing the risk of OHSS.	For FP, encourage women to attend at as young an age as possible. A good response to OS for a fresh embryo transfer is around 10–15 oocytes (Drakopoulos *et al.*, 2016). In FP, where an agonist trigger will be used and no embryo transfer will be performed, a higher target may be achievable. Oocyte pooling is an option in poor responders—patients may opt to do more than one cycle of OS and accumulate oocytes until a reasonable number is achieved.	Use simple OS protocols that require minimal visits to hospital. Easy-to-administer, subcutaneous, self-injected gonadotrophins simplify patients' experience. Random start OS and dual stimulation protocols are options to optimize oocyte pooling in a short time interval (Blockeel *et al.*, 2019; Bourdon *et al.*, 2020a; Bosch *et al.*, 2020b). Avoid unnecessary tests: Hormonal panels do not add much value, unless ovarian response is suboptimal or excessive (Bosch *et al.*, 2020a). Try to minimize secondary effects. Use protocols that minimize risk of OHSS and painful symptoms (Bourdon *et al.*, 2017). In oestrogen-sensitive diseases, the addition of letrozole or tamoxifen may be discussed.

FP, fertility preservation; OHSS, ovarian hyperstimulation syndrome; OS, ovarian stimulation.

Deciding on the optimal approach to FP is highly challenging. Controlled studies evaluating long-term outcomes of FP and robust cost-effectiveness analyses are needed. Several areas require further investigation: to assess the impact of BGCs on future fertility; to identify women for whom FP interventions will allow them to store a sufficient quantity and quality of reproductive material to obtain a birth; and to determine which women will re-use their stored materials in the future. These factors must be weighed against the monetary, psychological costs and medical risks of the FP technique. The purpose is to identify beforehand women who will really benefit from FP, to render oocyte/ovarian freezing cost beneficial. This step is essential for both patients and the public health system and to avoid health inequities.

Conclusion

There is growing evidence to support the use of oocyte or ovarian tissue cryopreservation as interventions to preserve female fertility, not only in women with cancer about to undergo gonadotoxic treatment but also in those with benign conditions, including BGCs. Although oocyte vitrification after OS is usually the preferred option, a number of FP strategies are available and may be adapted according to individual preference, perspectives, and the medical situation. Personalized FP counselling for women facing impending fertility loss is essential. Future studies should seek to establish how FP can best be applied in BGCs and to prospectively evaluate reproductive outcomes in different patient populations

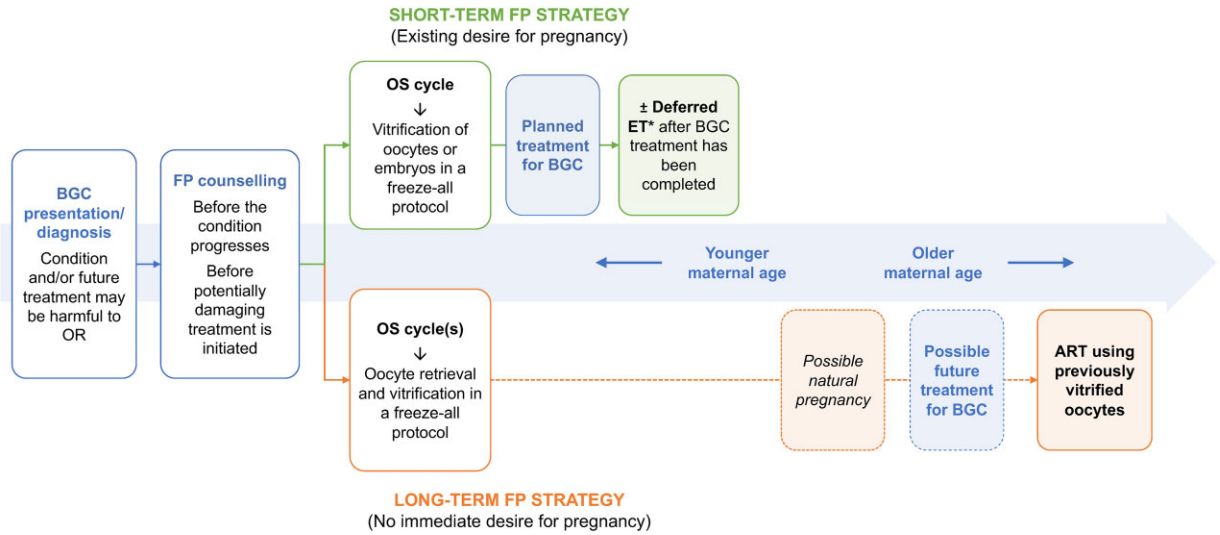

Figure 2. The ideal timing strategy for fertility preservation in women with benign gynaecological conditions. For women with BGCs, treatment that has the potential to be harmful to ovarian reserve and result in reduced fertility may be required at some time during their reproductive life; however, it may not be known if and when such treatment is likely to occur. *In the absence of natural conception. BGC, benign gynaecological condition; ET, embryo transfer; FP, fertility preservation; OS, ovarian stimulation; OR, ovarian reserve.

following ART with cryopreserved gametes. In the context of BGCs, cost-beneficial and cost-effectiveness issues should also be considered in the future, in order to better assess and select patients who will return to utilize their oocytes or ovarian tissue to become pregnant.

Data availability

No new data were generated or analysed in support of this research.

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Authors' roles

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