ELSEVIER

JMIG The Journal of Minimally Invasive Gynecology

Review Article

The Role of Fertility Preservation in Women with Endometriosis: A Systematic Review

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ABSTRACT **Objective:** To summarize the available evidence concerning fertility preservation techniques in the context of women with endometriosis.

Data Sources: We searched for studies published between 1984 and 2019 on endometriosis and Assisted Reproductive Technology outcomes. We searched MEDLINE and PubMed and performed a manual search of reference lists within identified studies.

Methods of Study Selection: A total of 426 articles were identified, and 7 studies were eligible to be included for the systematic review. We included all published studies, excluding reviews, case reports, and animal studies.

Tabulation, Integration, and Results: Despite a significant increase in the number of studies addressing fertility preservation over the study period, we found a relative lack of evidence addressing the use of fertility preservation techniques in women with endometriosis. The studies identified included 2 case reports, 1 histological science study, and 4 retrospective cohort studies.

Conclusion: Women with endometriosis may benefit from fertility preservation techniques. However, there currently is a paucity of data in this population, especially when compared with other indications for fertility preservation. Although much knowledge can be translated from the oncofertility discipline, we have identified and discussed endometriosis-related changes to ovarian reserve and oocyte health that justify further well-designed research to confirm that fertility preservation outcomes are similar for women with endometriosis. Journal of Minimally Invasive Gynecology (2020) 27, 362−372. © 2019 AAGL. All rights reserved.

Keywords: AMH; Endometriosis; Fertility preservation; Oocyte cryopreservation; Ovarian tissue cryopreservation

Fertility preservation in the form of embryo and oocyte freezing has been used extensively for several years, and many papers have demonstrated the efficacy and safety of these methods [1−3]. More recently, the use of ovarian cortex tissue preservation has been accepted as a means of fertility preservation when ovarian hyperstimulation is not possible because of medical contraindication or in the prepubertal patient [1,4].

Recent advances in fertility preservation technologies have ignited a debate regarding acceptable indications for its use. Offering fertility preservation before treatment with gonadotoxic agents in oncological patients is already widely acknowledged as the standard of care [2]. Many other conditions have now been described where fertility preservation may be considered [1], including premature ovarian insufficiency [5,6] and to manage age-related fertility decline, especially in the context of facilitating a woman's desire to postpone childbearing, also referred to as "social egg freezing" [3,7,8]. Increasingly, endometriosis has also been discussed as 1 of the clinical indications for fertility preservation.

Endometriosis affects 5% to 10% of women of childbearing age. In its severe form, it can lead to infertility [9], with almost half of those affected unable to conceive naturally [10]. The rationale for fertility preservation in women with endometriosis stems from the fact that the disease itself and the surgical

Dr. Rombauts reports personal fees from Monash IVF Group, grants from Ferring Australia, personal fees from Ferring Australia, non-financial support from Merck Serono, non-financial support from MSD, non-financial support from Guerbet, outside the submitted work; and I am a minority shareholder and the Group Medical Director for Monash IVF Group, a provider of fertility preservation services. The authors declare that they have no other conflict of interest.

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Submitted June 14, 2019, Revised September 1, 2019, Accepted for publication September 16, 2019.
Available at www.sciencedirect.com and www.jmig.org

1553-4650/$ — see front matter
https://doi.org/10.1016/j.jmig.2019.09.780

treatment for it can impair future fertility. Severe endometriosis can result in decreased ovarian reserve with histological and biochemical evidence of follicular damage even without previous surgical interventions [11−18]. This outcome is further compounded by recurrent excisional and ablative procedures, which are commonly used to treat the symptoms of endometriosis at the detriment of functional ovarian tissue [19]. Furthermore, recurrence of endometriosis is frequent and approaches 50% after 5 years [20,21]. There is also a growing body of evidence suggesting that patients with severe endometriosis are at increased risk of developing malignancy [22,23].

Although the utility of fertility preservation is becoming more established, we aim to systematically review the literature on fertility preservation specifically in women with endometriosis. Herein, we summarize the best available data, identify gaps in our current knowledge and recommend areas for future research.

Methods

The review followed the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [24]. The study was prospectively registered with PROSPERO (CRD42019127237).

Search Strategy

A systematic search of PubMed/MEDLINE databases was performed independently by 2 reviewers (D.L. and Y.C.). We used the search terms "Endometriosis," "fertility preservation," "Anti-Mullerian Hormone," and "oocyte cryopreservation" as keywords to recover all possible publications. The search terms were tested to check that they effectively located the types of articles that are consistent with the inclusion criteria before searching MEDLINE.

Strategies for our electronic search at the PubMed database were the following combined MeSH terms and search words with details:

("Endometriosis"[MeSH Terms] OR "Endometriosis"[All Fields]) AND ("fertility preservation"[MeSH Terms] OR "fertility preservation"[All Fields] OR "Oocyte Retrieval"[MeSH Terms] OR "Egg Freezing"[All Fields] OR "Oocyte cryopreservation"[All Fields] OR "Oocyte Retrieval"[All Fields] OR "Anti-Mullerian Hormone"[MeSH Terms] OR "Anti-Mullerian Hormone"[All Fields] OR "Cryopreservation"[MeSH Terms] OR "Cryopreservation"[All Fields])

The reference lists of all retrieved articles were manually scrutinized to increase the likelihood of identifying all relevant studies. In addition, experts in the field and the collaborative group were asked about their knowledge of any unpublished studies.

Selection Criteria, Eligibility and Data Extraction

Article eligibility was assessed independently by 2 reviewers (D.L. and Y.C.), with a third reviewer (L.R.) available to resolve any discrepancies.

Eligibility assessment was based on published protocols, method sections from publications. We included all prospective and retrospective studies published in English as abstract or full text from January 1985 to April 2019. Articles that evaluated fertility before and after surgical treatments of endometriosis and those that evaluated the efficacy of fertility preservation before and after endometriosis surgery were included. Reviews and animal studies were excluded. One reviewer (D.L.) abstracted the data into tables, and another author (Y.C.) reviewed the data independently.

Results

As technology has improved and options have become more accessible, there has been a significant increase in the number of PubMed citations on fertility preservation (Fig. 1). This trend has been matched by the rise in opinion papers concerning fertility preservation in women with endometriosis. In the past 6 years, there have been 10 opinion papers published addressing fertility preservation in endometriosis [10,25−33]. Despite this, the number of original studies specifically looking at the effectiveness of fertility preservation technologies in women with endometriosis was low, suggesting that this is an area of emerging research focus.

A total of 426 studies were identified upon initial search, with 27 identified for review of the full-text article. Following exclusions, 7 eligible articles were identified (Fig. 2), which included 2 case reports, 1 histological science study, and 4 retrospective cohort studies. There were no randomized controlled trials or prospective studies identified in our extensive search. These articles are summarized in Table 1.

Discussion

Our search of the published medical literature has highlighted the paucity of research on fertility preservation, specifically for women with endometriosis. The emerging evidence summarized here shows that more research is urgently needed because conclusions drawn from fertility preservation studies in women with healthy ovarian function may not be valid in women with endometriosis.

Endometriosis and Infertility

The association between endometriosis and infertility has long been established [1]. The mechanism behind this is likely multifactorial, and several pathways have been proposed for the pathogenesis of endometriosis-related infertility. Pelvic adhesions, caused primarily by the disease but also as the result of surgery, can cause a mechanical barrier at the tubo-ovarian interface. Many other postulated mechanisms by which endometriosis may impair fertility have been reviewed elsewhere and include intraperitoneal inflammation, which may lead to a microenvironment that is unfavorable for normal implantation [12], oxidative stress [16−18], and gonadotoxic concentrations of iron within the peritoneal

Fig. 1

The number of publications per year on fertility preservation according to a MEDLINE search using the term "fertility preservation" [MeSH Terms] OR "fertility preservation."

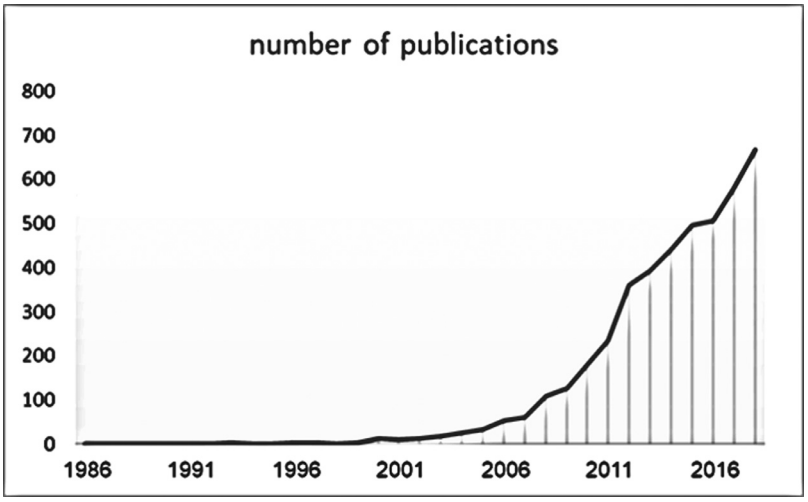
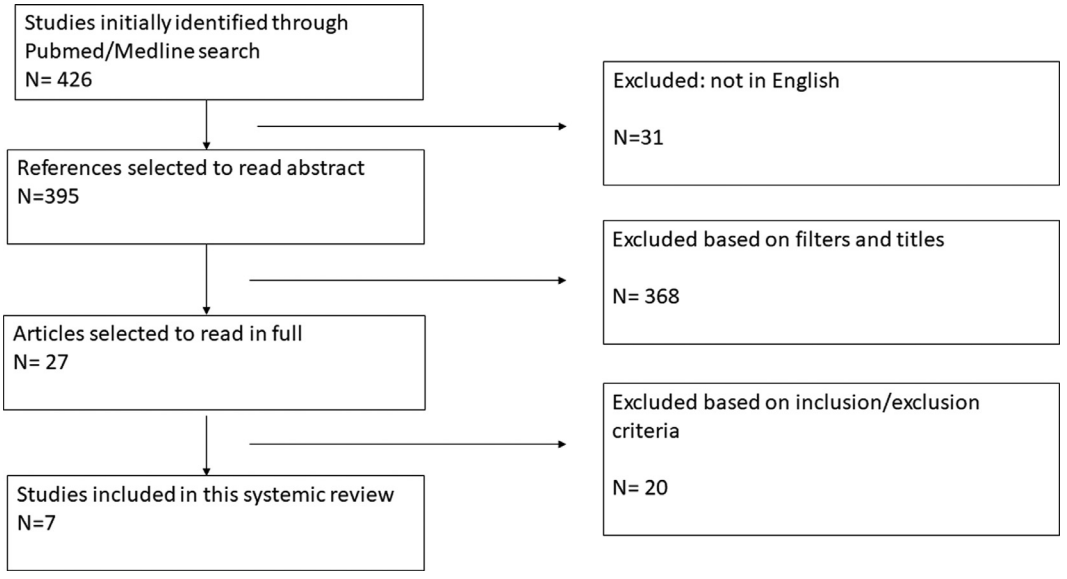


Fig. 2

Flow diagram of a systemic search of the literature.



cavity [13]. Importantly, it is now also becoming apparent that endometriosis reduces the ovarian reserve.

The Impact of Endometriosis on Ovarian Reserve

Oocyte Number

Women with endometriosis experience a progressive loss of ovarian reserve thought to be because of enhanced follicular recruitment and atresia [41]. Tissue adjacent to an endometrioma demonstrates morphological changes suggestive of poor follicular function and reduced follicular density [14]. This drop-in functional oocyte number indicates a fundamental reason for the associated decline in ovarian reserve.

A recent meta-analysis demonstrated that ovarian reserve before surgery, as measured by antimullerian hormone (AMH), is significantly reduced in women with unoperated endometriomas compared with women with no endometriomas (mean difference, −0.84, with 95% confidence interval, −1.16 to −0.52) [42]. A longitudinal prospective cohort study reported that women with endometriomas but no history of surgical management were found to experience menopause at an

Table 1

Original research on fertility preservation in endometriosis patients

Study	Study design	Study aim	Inclusion criteria	Results	Limitations
Garavaglia et al, 2017 [34]	Retrospective case-control study	To evaluate presurgical serum AMH levels in endometriosis patients undergoing OTCP for fertility preservation To correlate the preoperative AMH with the individual follicular density	202 Premenopausal women with endometriosis undergoing surgery for the first time 200 Healthy historic controls for serum AMH comparison 33 Control biopsies from ovaries without endometriosis	AMH levels were significantly lower in cases, but only for women >36 years old. No statistically significant difference in primordial or primary follicle numbers between cases and controls	2 different AMH assays used. Insufficient power
Raad et al, 2018 [35]	Retrospective cohort study	To describe a historic cohort of endometriosis patients having undergone oocyte cryopreservation	49 women who have endometriosis (mean age, 33.9 ± 4.5 years)	Mean oocytes recovered: Endometrioma excision vs no excision (11.2 ± 6.5 vs. 6.8 ± 4.4; p <.01) Mean mature oocytes recovered: Endometrioma excision vs no excision (8.3 ± 5.2 vs 5.3 ± 3.7; p <.01)	No healthy controls. No report on pregnancy outcomes or risks
Garcia-Velasco et al, 2013 [36]	Retrospective cohort study	To evaluate the results of controlled ovarian hyperstimulation for oocyte cryopreservation to preserve fertility for medical and non-medical indications (including 38 women with endometriosis)	560 non-oncological patients and 475 oncological patients	N/A	Not possible to extract data for endometriosis patients separately
Kuroda et al, 2019 [37]	Retrospective cohort study	To determine predictive factors for clinical outcomes of surgery; ART/hybrid therapy in infertile women with DOR with uterine fibroids and ovarian endometriomas	39 women with DOR (AMH <1.0 and advance age >40) requiring surgery for uterine myomas and endometriomas	14/39 (35.9%) women achieved a live birth with surgery-ART/hybrid therapy. Women achieving a live birth were significantly younger (median age 40 years [IQR, 38−41 years] vs 41.5 years [IQR, 41−42 years]; p = .032) and had significantly more frozen embryos available (5.0 [range, 4.0−6.0] vs 2.0 [range, 1.0−3.0]; p <.001). The serum AMH levels of both groups were not statistically different	Small study size. Not possible to extract data for endometriosis patients separately
Elizur et al, 2009 [38]	Case report	First report of fertility preservation in an endometriosis patient using oocyte cryopreservation	25-year-old nulliparous woman with severe endometriosis, recurrent surgeries, and low AFC	After 3 cycles of ovarian stimulation, 21 oocytes were cryopreserved	Single case. No report on pregnancy outcomes or risks

Table 1

Continued

Study	Study design	Study aim	Inclusion criteria	Results	Limitations
Donnez et al, 2005 [39]	Case report	To assess survival of primordial follicles in OTCP and reimplantation in endometriosis patients	2 patients with severe endometriosis undergoing oophorectomy for recurrent endometriosis	3 months after reimplantation: Viable primordial follicles present and neovascular capillary network present	Single case. No report on pregnancy outcomes or risks
Schubert et al, 2005 [40]	Basic science research: histological and viability analysis	To define whether the use of human ovarian cortex surrounding benign cysts is an appropriate model to study OTCP	25 premenopausal women with dermoid (n = 7), endometriosis (n = 13) and serous (n = 5) cysts	*Surrounding median follicular density* Dermoid vs serous vs endometrioma (13.04 vs 0.89 vs 0.31) *Surrounding median follicular viability* Dermoid vs serous vs endometrioma (2.93 vs 0.71 vs 0.05) Freezing and thawing: slightly decreased density of viable of follicles	Small study size. Significant variability between samples (CV = 35 % for histological analysis and 52% for viability analysis)

AFC = antral follicle count; AMH = antimullerian hormone; ART = assisted reproductive technology; CV = coefficient of variance; DOR = diminished ovarian reserve; IQR = interquartile range; OTCP = ovarian tissue cryopreservation.

earlier age compared with women without disease (median age 42.1 ± 5.1 years vs 47.1 ± 3.5 years; p = .003) [43], which supports our findings.

Oocyte Quality and Steroidogenesis

In addition to the effect on the number of remaining oocytes, endometriosis reduces oocyte quality. The seminal work by Simon et al [44] demonstrated that patients with endometriosis had the same chance of implantation and pregnancy as healthy recipients when transferred embryos were derived from oocytes donated by women without endometriosis. In contrast, healthy patients who received embryos derived from oocytes donated by women with endometriosis showed a significantly reduced implantation rate. Other authors have demonstrated similar findings, highlighting the direct impact of endometriosis on oocyte quality [45].

There is sufficient molecular, histological, and morphological evidence to support a harmful effect of an endometrioma on neighboring ovarian cortical tissue; an effect that is independent of mechanical stretching of the ovarian cortex owing to the size of the endometrioma [11]. One explanation is the high concentration of gonadotoxic free iron, which is released from an endometrioma on perforation [13]. Oocytes retrieved from women affected by endometriosis are also more likely to show altered morphology, lower cytoplasmic mitochondrial content [46], and spindle disruption [17,18] compared with women with other causes of infertility. Endometriosis-related inflammation within the ovary, evidenced by the presence of inflammatory cytokines such as IL- 12 in the peritoneal fluid [47,48] but also in the follicular fluid [49], further contribute to decreased oocyte quality. Comparison of follicular fluid samples from 200 women with advanced-stage endometriosis and 140 normal ovulating women during oocyte retrieval indicated that elevated IL-8, IL-12, and adrenomedullin concentrations in women with endometriosis are associated with poor oocyte and embryo quality [50].

Endometriosis also adversely affects the endocrine function of the ovarian follicle. Granulosa cell steroidogenesis is impaired in women with endometriosis through reduced expression of P450 aromatase [12], a key enzyme in the estradiol synthesis pathway.

The Impact of Surgery

In addition to the intrinsic damage to oocyte quantity and quality caused by endometriosis, endometriosis surgery itself presents a critical but modifiable risk factor. Surgical excision and ablation of ovarian endometriosis result in the removal or direct injury of the healthy adjacent cortex, potentially compromising ovarian blood supply [51,52]. It is becoming increasingly evident that ovarian cystectomy for endometriomas can cause considerable damage to ovarian reserve [53,54]. For example, in women with unilateral endometriomas, ovulation occurs less frequently from the ovary subjected to a cystectomy [55]. A recent meta-analysis has demonstrated a 59% reduction in AMH 6 months following surgical

excision of ovarian endometriomas [56]. It has been demonstrated that the decline in ovarian reserve markers following surgery is proportional to the severity of the endometriosis and certainly more prominent when bilateral endometrioma resection is performed [53,57]. Although AMH concentrations may recover slightly in the first months after surgery, they remain lower than preoperative concentrations [52,58]. In addition, repeat surgery causes further damage to the ovarian reserve [59]. Interestingly, the postoperative decrease in AMH does not appear to correlate with the amount of healthy ovarian tissue inadvertently excised with the endometrioma wall [56], indicating that the decline in AMH is more likely owing to vascular compromise.

Despite the impact of surgical management of ovarian endometriosis on future fertility, many women with endometriosis also suffer from debilitating pain [60,61]. Therefore, the benefits of symptom relief and restoration of the pelvic anatomy need to be weighed against the risk of a marked, seemingly permanent, reduction of ovarian reserve [62]. When patients and clinicians agree that this balance tips in favor of surgery, careful consideration needs to be given to the surgical technique.

First Do No Harm

Where surgery cannot be avoided, 'ovary-sparing' surgical techniques are the best prophylaxis and play a crucial role in the fertility outcome after surgery [52].

Systematic reviews published in 2008 and 2013 concluded that excisional surgery for endometriomas is less likely to result in recurrence of the endometrioma and pain symptoms, while, in women who were previously subfertile, it improves the chance of spontaneous pregnancy [63,64]. However, it should be remembered that the amount of functioning ovarian tissue that is removed together with the cyst wall is inversely related to the level of surgical experience [52,65]. This finding has led some authors to recommend other techniques such as the drainage and laser vaporization of the cyst wall without stripping or a combination of stripping and laser vaporization at the hilum as less detrimental to the ovary [52].

Achieving hemostasis following a cystectomy is another point of concern. Excessive electrocoagulation for hemostasis during laparoscopic excision of endometriomas is associated with a substantial reduction in ovarian reserve [49,66,67] and should be avoided where possible. The application of a hemostatic sealant and suturing to achieve hemostasis after laparoscopic cystectomy of ovarian endometriomas has a lesser impact on ovarian reserve compared with other laparoscopic techniques [68,69].

Fertility Preservation Options

Fertility preservation was developed to provide an option for future fertility to women undergoing gonadotoxic cancer treatment. With improving technology, reducing costs, increased acceptability and clinical experience, fertility preservation now finds broader indications including the management of age-related decline in egg quality and quantity [7]. Some of the treatment modalities of fertility preservation, such as oocyte freezing, have matured from an experimental technique into an established clinical practice [27].

Oocyte and Embryo Cryopreservation

Oocyte cryopreservation is a relatively new option that involves the harvesting of oocytes following an ovarian stimulation cycle and the careful cryopreservation with vitrification protocols that have been adapted from embryo freezing techniques [3,36,38]. The vitrification of embryos is also possible and occurs after the retrieved oocytes have been successfully fertilized with sperm. There are no known biological limits to how long they can be stored, provided they are kept under tightly controlled conditions [35].

Cryopreservation of oocytes has become a widely adopted technique for fertility preservation because (1) this technique does not require a male partner, and (2) has been accepted by major societies as a clinically validated technique [70]. Principally, this is because cryopreserved oocytes perform virtually the same as fresh oocytes [71] since modified vitrification techniques were introduced [35].

Although the chances of a live birth using vitrified oocytes rapidly decline after the age of 36 years [72,73], we have not found any studies that reported more specifically on endometriosis being an additional factor determining the final outcome. Given the concerns, as mentioned earlier regarding oocyte quality, there is a strong need for further research in this area.

Arguably, embryos are less vulnerable than oocytes to the stresses of vitrification, but the survival of vitrified oocytes has improved to the point where this is less of a decisive factor. Indeed, the ethical aspects of cryopreserving human embryos versus oocytes are different, and this should be taken into consideration, especially where there is no intention to replace the embryos in the short to medium term. In a setting where a change in social circumstances is not unlikely, cryopreserved oocytes also provide a more flexible option and can be thawed and fertilized with the gametes of the partner at the time.

Oocyte Cryopreservation in Women with Endometriosis

The first report of fertility preservation in endometriosis was published by Elizur et al [74] in 2009. This case was a report of a 25-year-old woman who underwent successful oocyte cryopreservation from her remaining ovary after having had 4 surgeries to treat endometriosis-related symptoms. Although this patient was reported to have a low antral follicle count of 3, after 3 ovarian stimulation cycles, she had 29 oocytes aspirated, 21 of which were mature and subsequently cryopreserved.

Raad et al [35] published their preliminary data regarding 49 endometriosis patients aged 21 to 40 years, who underwent oocyte cryopreservation at their institute. The

cohort was divided into 3 subgroups according to their endometriosis phenotype: superficial and deep peritoneal disease or the presence of an endometrioma. The mean number ± standard deviation of recovered and cryopreserved oocytes per cycle was 9.5 ± 6.1 and 7.2 ± 4.9, respectively. These parameters were significantly lower in patients reporting previous endometrioma excision when compared with those without ovarian surgery (6.8 ± 4.4 vs 11.2 ± 6.5 oocytes recovered; p <.01; and 5.3 ± 3.7 vs. 8.3 ± 5.2 cryopreserved oocytes; p <.01). These findings are in line with previous articles [75−77], as well as a recent meta-analysis in this journal [78], showing that following endometrioma surgery the total number of oocytes retrieved was lower in the surgery group (mean difference, −1.51; 95% confidence interval, −2.60 to −0.43; p = .02).

As cryopreservation of oocytes and embryos requires significant exogenous hormone administration, there is a theoretical concern regarding the worsening of the endometriosis if it has not been treated surgically. However, repeated controlled ovarian hyperstimulation cycles for treatment of infertility have not been associated with an increased risk for recurrence of endometriosis [79−81].

Ovarian Downregulation

Many recently published studies support the use of gonadotropin-releasing hormone (GnRH) agonists before and during chemotherapy to reduce the risk of premature ovarian insufficiency and increase the probability of spontaneous live birth in the short term [82−84]. It is believed that GnRH agonists can keep primordial follicles in a dormant state through central inhibition as a result of reducing their susceptibility to the harmful effects of chemotherapy. The progressive loss of ovarian reserve because of enhanced follicular recruitment and atresia is also seen in women with endometriosis [41] and is aggravated by damage during surgery. There have been sporadic and conflicting reports with some supporting the use of GnRH agonists after bilateral endometrial cystectomy, citing improved pregnancy rates and ovarian reserve and reduced recurrence [85]. Others have demonstrated a negative effect of this type of treatment on pregnancy rates [86]. Therefore, although ovarian downregulation is a broadly accepted practice in the context of fertility preservation in women undergoing chemotherapy, its utility in women with endometriosis is another area that requires further research.

Ovarian Tissue Cryopreservation

A healthy ovarian cortex contains thousands of primordial follicles that have the potential to grow to dominant follicles holding mature oocytes [87]. Ovarian tissue cryopreservation (OTCP) involves taking 1 or more biopsies from healthy ovarian tissue, typically via laparoscopy. Stromal components are then removed from cortical tissue, which is then aliquoted into separate cryopreservation vials and vitrified [1,39,88−90].

Fertility can be restored by transplanting the tissue onto remaining ovarian tissue or into the ovarian fossa in order to optimize the benefits of physiological paracrine activity [91]. When this is not possible, for example after bilateral oophorectomy [92], transplantation under the skin of the abdominal wall, forearm, or breast has all been attempted [93,94]. The key barrier to this technique is the ischemic stress experienced by cortical tissue upon thawing which can result in a 50% to 75% reduction in the number of follicles [95,96].

Since the first pregnancy reported from auto-transplanted ovarian tissue in 2004, [97] and the second in 2005 [4], there have been over 130 births worldwide [1] with a published success rate of 30% after auto-transplantation [98,99]. Although some are calling for this technique to be more routinely adopted [100], this procedure is still considered experimental by the American Society for Reproductive Medicine [101], American Society of Clinical Oncology [102], European Society for Human Reproduction and Embryology [103] and European Society for Medical Oncology [104]. Hence, in a clinical setting, OTCP is currently reserved for situations where oocyte or embryo freezing is not an option, such as (1) prepubertal women, (2) when gonadotoxic treatment cannot be postponed, and (3) when exogenous hormonal exposure can aggravate the underlying condition.

A combination of ovarian stimulation for oocyte cryopreservation, followed by OTCP has also been described for oncofertility preservation with promising results [105]. OTCP followed by controlled ovarian stimulation and oocyte retrieval increased overall fertility preservation without impairing the number or quality of cryopreserved embryos [106].

It has been over 20 years since the first report of the successful isolation of primordial follicles from fresh and cryopreserved human ovarian tissue [107]. Future prospective studies using isolated primordial and primary follicles grown within biomaterial matrices either in vitro or in vivo may ultimately provide a further means to preserve fertility in premenopausal patients. These techniques are already showing promising results in animal models with the successful delivery of healthy pups [108]. These developments have improved our ability to isolate a higher number of developmentally competent follicles for fertility preservation with the ultimate goal of creating an artificial ovary [109,111]. The considerable advantage of this approach is the elimination of the risk of reseeding cancerous cells within the biopsy. In the future, it may also become a viable option for other indications, including endometriosis, as a way to avoid the ischemia-induced follicular atresia after transplantation of whole ovarian tissue.

OTCP in Women with Endometriosis

OTCP has been utilized in the context of endometriosis as early as 2005. Only 1 year after Donnez et al [97] reported the first birth after an ovarian tissue transplant, a case report by the same author described 2 patients who underwent unilateral

oophorectomy for recurrent endometriosis. The healthy cortex was resected and implanted in the orthotopic site during the same procedure. After 3 months of GnRH treatment, a biopsy taken from the grafted tissue 3 months later demonstrated viable ovarian tissue with neovascularization of primordial follicles. The first patient underwent IVF and managed to conceive [39]. Another report also noted endocrine changes associated with follicular growth and ovulation after transplantation in women with endometriosis [112].

Theoretically, the process of freezing and thawing ovarian cortical tissue could damage the healthy follicles contained within it, especially in women with endometriosis who might already have impaired oocyte quality. However, when healthy cortical tissue adjacent to an endometrioma is cryopreserved, the freeze-thaw process does not result in significant atresia of the follicles, but there is a decrease in the density of viable follicles [40].

This comprehensive systematic review identified only 2 case reports, 1 histological science study, and 4 retrospective cohort studies focusing specifically on fertility preservation in women with endometriosis. There were no articles with randomized controlled trials or prospective study design. Largely, the lack of research in this area may reflect the fact that fertility preservation, in particular ovarian tissue freezing, is predominantly considered in cancer patients, from where most of the research originates. Much of the literature we identified borrowed heavily from the field of oncofertility and extrapolated from existing clinical, histological, and biochemical research on how it may apply to women with endometriosis.

Specific reasons why women with endometriosis should be counseled about fertility preservation options relate to clinical presentations where oophorectomy and extensive ovarian surgery cannot be avoided. Although neither oocyte and embryo freezing nor ovarian tissue freezing provides any future guarantees of live birth, there are potentially medico-legal implications in not offering fertility preservation in women at risk of iatrogenic ovarian failure. Although the risk of ovarian cancer is increased in women with endometriosis, the absolute risk remains relatively low and identifying those who are at highest risk for cancer conversion remains a challenge.

Personalized fertility preservation counseling of women with endometriosis should take into consideration the patient's age, the severity of disease, the presence of endometriomas and the history of priory surgery. However, our review has highlighted the lack of reliable data on success rates and safety of fertility preservation in this population. Success rates should, therefore, be quoted carefully, as fertility preservation for other indications may not reflect the same outcomes as in patients with endometriosis.

This paucity of information regarding the utility of fertility preservation in women with endometriosis is somewhat surprising given our growing understanding that this disease significantly impacts ovarian function and reserve. Key areas or future research should, therefore, focus on the following 3 priorities. Firstly, we need to deepen our understanding of the pathophysiological mechanisms that lead to decline in oocyte quantity and quality. Do these effects only act locally within the ovary or does it affect women with peritoneal disease as well? What are the modifiable risk factors of fertility loss in women with endometriosis? Secondly, we need to develop techniques of fertility preservation that account for the altered ovarian physiology in women with endometriomas. Finally, we need to prospectively document success rates and health outcomes of babies born following fertility preservation techniques in women with endometriosis, ideally in conjunction with an existing international registry such as the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project initiative [110].

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