The role of fertility preservation in women with endometriosis: a systematic review

Daniel Lantsberg MD MHA ,
Shavi Fernando MBBS(hons) BMedSc(hons) PhD ,
Yoni Cohen MD PhD , Luk Rombauts MD PhD

PII: S1553-4650(19)31207-5
DOI: https://doi.org/10.1016/j.jmig.2019.09.780
Reference: JMIG 3960

To appear in: *The Journal of Minimally Invasive Gynecology*

Received date: 14 June 2019
Revised date: 1 September 2019
Accepted date: 16 September 2019

Please cite this article as: Daniel Lantsberg MD MHA , Shavi Fernando MBBS(hons) BMedSc(hons) PhD , Yoni Cohen MD PhD , Luk Rombauts MD PhD , The role of fertility preservation in women with endometriosis: a systematic review, *The Journal of Minimally Invasive Gynecology* (2019), doi: https://doi.org/10.1016/j.jmig.2019.09.780

The role of fertility preservation in women with endometriosis: a systematic review.

Daniel Lantsberg MD MHA, Shavi Fernando MBBS(hons) BMedSc(hons) PhD, Yoni Cohen MD PhD, Luk Rombauts MD PhD

From the Department of Obstetrics and Gynecology, Monash University, Clayton Australia (Prof. Rombauts and Dr. Fernando), Women's Health, Monash Health, Clayton Australia 3168 (Prof. Rombauts and Dr. Fernando), Monash IVF Group, Richmond Australia, 3121 (Prof Rombauts) and from Department of Obstetrics, Gynecology and fertility, Lis Maternity Hospital (Drs. Lantsberg and Cohen), Sourasky Tel-Aviv medical center and from Sackler Faculty of Medicine (Drs. Lantsberg and Cohen), Tel-Aviv University, Israel.

Corresponding author:

Daniel Lantsberg MD MHA

Department of Obstetrics and Gynecology, Lis Maternity Hospital, Tel-Aviv Sourasky Medical Center 6 Weizman Rd, Israel.Email: daniel.lantsberg@gmail.com

Telephone +972 54 2472775

Disclosure statement: D.L., S.F. and Y.C. declare that they have no conflict of interest and nothing to disclose. L.R. has declared potential conflicts of interest.

Precis

Women with endometriosis may benefit from fertility preservation techniques but endometriosis-related changes to ovarian reserve and oocyte health justify further research.

Abstract

STUDY OBJECTIVE: To summarise the available evidence concerning fertility preservation techniques in the context of women with endometriosis.

DATA SOURCES: We searched studies published between 1984 and 2019 on endometriosis and ART outcome. 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, one histological science studies and four 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 to other indications for fertility preservation. While much knowledge can be translated from the oncofertility discipline, we have identified and discuss 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.

Key words

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

INTRODUCTION

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 due to a 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 prior to 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 one of the clinical indications for fertility preservation.

Endometriosis affects 5-10% 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 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 (11-19). This 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 (20). Furthermore, recurrence of endometriosis is common and approaches 50% after five years (21, 22). There is also a growing body of evidence suggesting that patients with severe endometriosis are at increased risk of developing malignancy (23, 24).

While 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 summarise 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 (25) 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 key words 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 prior to conducting the search on 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])

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

Selection Criteria, Eligibility and Data Extraction

Study eligibility was assessed independently by two 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. Studies 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

(Figure 1). This trend has been matched by the rise in opinion papers concerning fertility preservation in women with endometriosis. Only in the past six years, there have been 10 opinion papers published addressing fertility preservation in endometriosis (10, 26-34).

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 intial search, with 27 identified for review of the full text article. Following exclusions, seven eligible studies were identified (Figure 2). This included 2 case reports, one histological science study and four retrospective cohort studies. There were no RCTs or prospective studies identified in our extensive search. These studies are summarised 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 to be 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 (17, 35, 36) and gonadotoxic concentrations of iron within the peritoneal cavity (37). 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 due to enhanced follicular recruitment and atresia (38). Tissue adjacent to an endometrioma demonstrates morphological changes suggestive of poor follicular function and reduced follicular density (15). This drop in functional oocyte number indicates an intrinsic reason for the associated decline in ovarian reserve. A recent meta-analysis demonstrated that ovarian reserve prior to surgery, as measured by AMH, is significantly reduced in women with unoperated endometriomas compared to women with no endometriomas (mean difference -0.84, with 95% confidence interval [CI] -1.16 to -0.52) (39). Supporting this finding, a longitudinal prospective cohort study found that women with endometriomas but no history of surgical management were found to experience menopause at an earlier age compared to women without disease (median age 42.1 +/- 5.1 years versus 47.1 +/- 3.5 years, P = 0.003) (40).

Oocyte quality and steroidogenesis

In addition to the effect on the quantity of remaining oocytes, endometriosis has a negative impact on oocyte quality. The seminal work by Simon et al. (41) demonstrated that patients with endometriosis have 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 (42). 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 due 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 (43) and spindle disruption (35, 36) compared to 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 (44, 45) but also in the follicular fluid (46), 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 (47).

Endometriosis also has an adverse effect on 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 an important but modifiable risk factor. Surgical excision and/or ablation of ovarian endometriosis results in the removal or direct injury of healthy adjacent cortex potentially compromising ovarian

blood supply (48, 49). It is becoming increasingly evident that ovarian cystectomy for endometriomas can cause considerable damage to ovarian reserve (50-52). In women with unilateral endometriomas, for example, ovulation occurs less frequently from the ovary subjected to a cystectomy (53). A recent meta-analysis has demonstrated a 59% reduction in AMH six months following surgical excision of ovarian endometriomas (54). 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 preformed (50, 55). Although AMH concentrations may recover slightly in the first months after surgery, they remain lower than preoperative concentrations (56, 57). Additionally, repeat surgery causes further damage to the ovarian reserve (58). Interestingly, the postoperative decrease in AMH does not appear to correlate with the amount of healthy ovarian tissue inadvertently excised with the endometrioma wall (54), indicating that the decline in AMH is more likely due to vascular compromise.

Despite the impact of surgical management of ovarian endometriosis on future fertility, many women with endometriosis also suffer from debilitating pain (59, 60). Therefore, the benefits of symptom relief and restoration of the pelvic anatomy clearly need to be weighed against the risk of a marked, seemingly permanent, reduction of ovarian reserve (61). When patient and clinician agree that this balance tips in favour 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 (49). 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 (64, 65). It should be remembered, however, that the amount of functioning ovarian tissue that is removed together with the cyst wall has been shown to be inversely related to the level of surgical experience (49, 49, 66), which 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 (51).

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 (48, 67, 68) and should be avoided where possible. The application of a hemostatic sealant and suturing to achieve hemostasis after laparoscopic cystectomy of ovarian endometriomas have a lesser impact on ovarian reserve compared with other laparoscopic techniques (69, 70).

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 (28).

Oocyte/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, 72, 73). 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 regulated conditions (74).

Cryopreservation of oocytes has become a widely adopted technique for fertility preservation because a) this technique does not require a male partner and b) has been accepted by major societies as a clinically validated technique (75). Principally, this is because cryopreserved oocytes perform virtually the same as fresh oocytes (76) since modified vitrification techniques were introduced (74).

While the chances of a live birth using vitrified oocytes rapidly decline after the age of 36 years (77, 78), we have not found any studies that reported more specifically on endometriosis being an additional factor determining the final outcome. Given the aforementioned concerns regarding oocyte quality, there is clearly 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. Certainly, 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. (79) in 2009. This was a case report of a 25 year old woman who underwent successful oocyte cryopreservation from her remaining ovary after having previously had four surgeries to treat endometriosis-related symptoms. Although this patient

was reported to have a low AFC of 3, after three ovarian stimulation cycles she had 29 oocytes aspirated, 21 of which were mature and subsequently cryopreserved. Raad at el. published their preliminary data regarding 49 endometriosis patients aged 21-40, who underwent oocyte cryopreservation at their institute (80). The cohort was divided into three subgroups according to their endometriosis phenotype: superficial and deep peritoneal disease or the presence of an endometrioma. The mean number of recovered and cryopreserved oocytes per cycle was 9.5 $\pm$ 6.1 and 7.2 $\pm$ 4.9, respectively. These parameters were significantly lower in patients reporting previous endometrioma excision when compared with those without ovarian surgery (6.8 $\pm$ 4.4 vs. 11.2 $\pm$ 6.5 oocytes recovered, $p < 0.01$ and 5.3 $\pm$ 3.7 vs. 8.3 $\pm$ 5.2 cryopreserved oocytes, $p < 0.01$). These findings are in line with other studies (81-83) and a recent metanalysis in this journal (84), showing that following endometrioma surgery the total number of oocytes retrieved was lower in the surgery group (mean difference = 1.51; 95% CI, -2.60 to -0.43; $p = 0.02$).

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 (85-87).

Ovarian downregulation

Many recently published studies support the use of GnRH agonists before and during chemotherapy to reduce the risk of premature ovarian insufficiency (POI) and increase the probability of spontaneous live birth in the short term (88-90). It is believed that GnRH agonists can keep primordial follicles in a dormant state through central inhibition hereby reducing their susceptibility to the harmful effects of chemotherapy. Progressive loss of ovarian reserve due to enhanced follicular recruitment and atresia is also seen in women with endometriosis (38) 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 (91). Others have demonstrated a negative effect of this type of treatment on pregnancy rates (92). Therefore, while ovarian downregulation is a largely 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 (OTCP)

Healthy ovarian cortex contains thousands of primordial follicles which have the potential to grow to dominant follicles holding mature oocytes (93). Ovarian tissue cryopreservation involves taking one 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, 94-96).

Fertility can be restored by transplanting the tissue onto remaining ovarian tissue or into the ovarian fossa in order to optimise the benefits of physiological paracrine activity (97). If this is not possible, for example after bilateral oophorectomy (98), transplantation under the skin of the abdominal wall, forearm or breast have all been attempted (99, 100).

The key barrier to this technique is the ischemic stress experienced by cortical tissue upon thawing which can result in a 50-75% reduction in the number of follicles(101, 102).

Since the first pregnancy reported from auto-transplanted ovarian tissue in 2004 (103) and the second in 2005 (4) there have been over 130 births worldwide (1) with a published success rate of 30% after auto-transplantation (104, 105). Despite the fact that some are calling for this technique to be more routinely adopted (105), this

procedure is still considered experimental by the ASRM (106), ASCO (107), ESHRE (108) and ESMO (109). Hence, in a clinical setting, ovarian tissue cryopreservation is currently reserved for situations where oocyte or embryo freezing are not an option, such as 1) prepubertal women, 2) when gonadotoxic treatment cannot be postponed or 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 onco-fertility preservation with promising results (110). OTCP followed by COH and oocyte retrieval increased overall fertility preservation without impairing the number or quality of cryopreserved embryos (111).

It has been over 20 years since the first report of the successful isolation of primordial follicles from fresh and cryopreserved human ovarian tissue (113). 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 (112). These developments have improved our ability to isolate a greater number of developmentally competent follicles for fertility preservation with the ultimate goal of creating an artificial ovary (114, 115). 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 one year after Donnez et al reported the first birth after an ovarian tissue transplant (103), a case report by the same author described two patients who underwent unilateral oophorectomy for recurrent endometriosis. 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 three months later demonstrated viable ovarian tissue with neovascularization of primordial follicles. The first patient underwent IVF and managed to conceive (94). Another report also noted endocrine changes associated with follicular growth and ovulation after transplantation in women with endometriosis (116).

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 major atresia of the follicles but there is a decrease in the density of viable follicles (117).

CONCLUSION

This comprehensive systematic review identified only 2 case reports, one histological science studies and four retrospective cohort studies focusing specifically on fertility preservation in women with endometriosis. There were no RCTs or prospective studies identified. 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, where most of the research originates from. Much of the literature we identified borrowed heavily from the field of onco-fertility 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 counselled about fertility preservation options relate to clinical presentations where oophorectomy and/or extensive ovarian surgery cannot be avoided. While neither oocyte/embryo freezing or ovarian tissue freezing provide any future guarantees of a live birth, there are potentially medico-legal implications in not offering fertility preservation in women at

risk of iatrogenic ovarian failure. While 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, 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 of future research should therefore focus on the following three 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. And 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 WERF EPHect initiative (118).

ACKNOWLEDGEMENT

The authors declare that did not receive any financial support for this review

1. Donnez J, Dolmans MM. Fertility Preservation in Women. *N Engl J Med*. 2018; 378:400-1.

2. De Vos M, Smitz J, Woodruff TK. Fertility preservation in women with cancer. *Lancet*. 2014; 384:1302-10.

3. Cobo A, Garcia-Velasco JA, Coello A, et al. Oocyte vitrification as an efficient option for elective fertility preservation. *Fertil Steril*. 2016; 105:764.e8.

4. Meirow D, Levron J, Eldar-Geva T, et al. Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. *N Engl J Med*. 2005; 353:318-21.

5. Grynberg M, Bidet M, Benard J, et al. Fertility preservation in Turner syndrome. *Fertil Steril*. 2016; 105:13-9.

6. Talaulikar VS, Conway GS, Pimblett A, et al. Outcome of ovarian stimulation for oocyte cryopreservation in women with Turner syndrome. *Fertil Steril*. 2019; 111:505-9.

7. Stoop D, Cobo A, Silber S. Fertility preservation for age-related fertility decline. *Lancet*. 2014; 384:1311-9.

8. Cobo A, Garcia-Velasco JA, Domingo J, et al. Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients?. *Fertil Steril*. 2013; 99:1485-95.

9. de Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. *Lancet*. 2010; 376:730-8.

10. Somigliana E, Viganò P, Filippi F, et al. Fertility preservation in women with endometriosis: for all, for some, for none?. *Hum Reprod*. 2015; 30:1280-6.

11. Sanchez AM, Vigano P, Somigliana E, et al. The distinguishing cellular and molecular features of the endometriotic ovarian cyst: from pathophysiology to the potential endometrioma-mediated damage to the ovary. *Hum Reprod Update*. 2014; 20:217-30.

12. Sanchez AM, Somigliana E, Vercellini P, et al. Endometriosis as a detrimental condition for granulosa cell steroidogenesis and development: From molecular alterations to clinical impact. *J Steroid Biochem Mol Biol*. 2016; 155:35-46.

13. Sanchez AM, Papaleo E, Corti L, et al. Iron availability is increased in individual human ovarian follicles in close proximity to an endometrioma compared with distal ones. *Hum Reprod*. 2014; 29:577-83.

14. Sanchez AM, Somigliana E, Vercellini P, et al. Endometriosis as a detrimental condition for granulosa cell steroidogenesis and development: From molecular alterations to clinical impact. *J Steroid Biochem Mol Biol*. 2016; 155:35-46.

15. Maneschi F, Marasa L, Incandela S, et al. Ovarian cortex surrounding benign neoplasms: a histologic study. *Am J Obstet Gynecol*. 1993; 169:388-93.

16. Singh AK, Chattopadhyay R, Chakravarty B, et al. Markers of oxidative stress in follicular fluid of women with endometriosis and tubal infertility undergoing IVF. *Reprod Toxicol*. 2013; 42:116-24.

17. Da Broi MG, Malvezzi H, Paz CCP, et al. Follicular fluid from infertile women with mild endometriosis may compromise the meiotic spindles of bovine metaphase II oocytes. *Hum Reprod*. 2014; 29:315-23.

18. Da Broi MG, de Albuquerque FO, de Andrade AZ, et al. Increased concentration of 8-hydroxy-2'-deoxyguanosine in follicular fluid of infertile women with endometriosis. *Cell Tissue Res*. 2016; 366:231-42.

19. Da Broi MG, Jordão AA, Ferriani RA, et al. Oocyte oxidative DNA damage may be involved in minimal/mild endometriosis-related infertility. *Mol Reprod Dev*. 2018; 85:128-36.

20. Benaglia L, Somigliana E, Vighi V, et al. Rate of severe ovarian damage following surgery for endometriomas. *Hum Reprod*. 2010; 25:678-82.

21. Guo SW. Recurrence of endometriosis and its control. *Hum Reprod Update*. 2009; 15:441-61.

22. Vercellini P, DE Matteis S, Somigliana E, et al. Long-term adjuvant therapy for the prevention of postoperative endometrioma recurrence: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2013; 92:8-16.

23. Torng PL. Clinical implication for endometriosis associated with ovarian cancer. *Gynecol Minim Invasive Ther*. 2017; 6:152-6.

24. Matalliotakis M, Matalliotaki C, Goulielmos GN, et al. Association between ovarian cancer and advanced endometriosis. *Oncol Lett*. 2018; 15:7689-92.

25. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009; 339:b2535.

26. Bedoschi G, Turan V, Oktay K. Fertility preservation options in women with endometriosis. *Minerva Ginecol*. 2013; 65:99-103.

27. Barnett R, Banks N, Decherney AH. Endometriosis and Fertility Preservation. *Clin Obstet Gynecol*. 2017; 60:517-23.

28. Carrillo L, Seidman DS, Cittadini E, et al. The role of fertility preservation in patients with endometriosis. *J Assist Reprod Genet*. 2016; 33:317-23.

29. Somigliana E. Ovarian reserve, endometriomas, and surgery: research must go on. *Fertil Steril*. 2018; 110:856-7.

30. Evans MB, Decherney AH. Fertility and Endometriosis. *Clin Obstet Gynecol*. 2017; 60:497-502.

31. Donnez J, García-Solares J, Dolmans M. Ovarian endometriosis and fertility preservation: a challenge in 2018. *Minerva Ginecol*. 2018; 70:408-14.

32. Donnez J, Squifflet J, Jadoul P, et al. Fertility preservation in women with ovarian endometriosis. *Front Biosci (Elite Ed)*. 2012; 4:1654-62.

33. Sönmezer M, Taşkın S. Fertility preservation in women with ovarian endometriosis. *Womens Health (Lond)*. 2015; 11:625-31.

34. Streuli I, Benard J, Hugon-Rodin J, et al. Shedding light on the fertility preservation debate in women with endometriosis: a swot analysis. *Eur J Obstet Gynecol Reprod Biol*. 2018; 229:172-8.

35. Da Broi MG, de Albuquerque FO, de Andrade AZ, et al. Increased concentration of 8-hydroxy-2'-deoxyguanosine in follicular fluid of infertile women with endometriosis. *Cell Tissue Res*. 2016; 366:231-42.

36. Da Broi MG, Jordao AA, Ferriani RA, et al. Oocyte oxidative DNA damage may be involved in minimal/mild endometriosis-related infertility. *Mol Reprod Dev*. 2018; 85:128-36.

37. Sanchez AM, Papaleo E, Corti L, et al. Iron availability is increased in individual human ovarian follicles in close proximity to an endometrioma compared with distal ones. *Hum Reprod*. 2014; 29:577-83.

38. Kitajima M, Dolmans MM, Donnez O, et al. Enhanced follicular recruitment and atresia in cortex derived from ovaries with endometriomas. *Fertil Steril*. 2014; 101:1031-7.

39. Muzii L, Di Tucci C, Di Feliciantonio M, et al. Antimullerian hormone is reduced in the presence of ovarian endometriomas: a systematic review and meta-analysis. *Fertil Steril*. 2018; 110:940.e1.

40. Coccia ME, Rizzello F, Mariani G, et al. Ovarian surgery for bilateral endometriomas influences age at menopause. *Hum Reprod*. 2011; 26:3000-7.

41. Simon C, Gutierrez A, Vidal A, et al. Outcome of patients with endometriosis in assisted reproduction: results from in-vitro fertilization and oocyte donation. *Hum Reprod*. 1994; 9:725-9.

42. Diaz I, Navarro J, Blasco L, et al. Impact of stage III-IV endometriosis on recipients of sibling oocytes: matched case-control study. *Fertil Steril*. 2000; 74:31-4.

43. Sanchez AM, Vanni VS, Bartiromo L, et al. Is the oocyte quality affected by endometriosis? A review of the literature. *J Ovarian Res*. 2017; 10:4.

44. Fairbanks F, Abrao MS, Podgaec S, et al. Interleukin-12 but not interleukin-18 is associated with severe endometriosis. *Fertil Steril*. 2009; 91:320-4.

45. Gazvani R, Templeton A. Peritoneal environment, cytokines and angiogenesis in the pathophysiology of endometriosis. *Reproduction*. 2002; 123:217-26.

46. Singh AK, Dutta M, Chattopadhyay R, et al. Intrafollicular interleukin-8, interleukin-12, and adrenomedullin are the promising prognostic markers of oocyte and embryo quality in women with endometriosis. *J Assist Reprod Genet*. 2016; 33:1363-72.

47. Singh AK, Dutta M, Chattopadhyay R, et al. Intrafollicular interleukin-8, interleukin-12, and adrenomedullin are the promising prognostic markers of oocyte and embryo quality in women with endometriosis. *J Assist Reprod Genet*. 2016; 33:1363-72.

48. Li CZ, Liu B, Wen ZQ, et al. The impact of electrocoagulation on ovarian reserve after laparoscopic excision of ovarian cysts: a prospective clinical study of 191 patients. *Fertil Steril*. 2009; 92:1428-35.

49. Muzii L, Marana R, Angioli R, et al. Histologic analysis of specimens from laparoscopic endometrioma excision performed by different surgeons: does the surgeon matter?. *Fertil Steril*. 2011; 95:2116-9.

50. Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2012; 97:3146-54.

51. Donnez J, Lousse JC, Jadoul P, et al. Laparoscopic management of endometriomas using a combined technique of excisional (cystectomy) and ablative surgery. *Fertil Steril*. 2010; 94:28-32.

52. Jadoul P, Kitajima M, Donnez O, et al. Surgical treatment of ovarian endometriomas: state of the art?. *Fertil Steril*. 2012; 98:556-63.

53. Horikawa T, Nakagawa K, Ohgi S, et al. The frequency of ovulation from the affected ovary decreases following laparoscopic cystectomy in infertile women with unilateral endometrioma during a natural cycle. *J Assist Reprod Genet*. 2008; 25:239-44.

54. Muzii L, Di Tucci C, Di Feliciantonio M, et al. Ovarian Reserve Reduction With Surgery Is Not Correlated With the Amount of Ovarian Tissue Inadvertently Excised at Laparoscopic Surgery for Endometriomas. *Reprod Sci*. 2019:1933719119828055.

55. Hirokawa W, Iwase A, Goto M, et al. The post-operative decline in serum anti-Mullerian hormone correlates with the bilaterality and severity of endometriosis. *Hum Reprod*. 2011; 26:904-10.

56. Chang HJ, Han SH, Lee JR, et al. Impact of laparoscopic cystectomy on ovarian reserve: serial changes of serum anti-Mullerian hormone levels. *Fertil Steril*. 2010; 94:343-9.

57. Muzii L, Di Tucci C, Di Feliciantonio M, et al. Ovarian Reserve Reduction With Surgery Is Not Correlated With the Amount of Ovarian Tissue Inadvertently Excised at Laparoscopic Surgery for Endometriomas. *Reprod Sci*. 2019:1933719119828055.

58. Jacob GP, Oraif A, Power S. When helping hurts: the effect of surgical interventions on ovarian reserve. *Hum Fertil (Camb)*. 2016; 19:3-8.

59. Kim JH, Han E. Endometriosis and Female Pelvic Pain. *Semin Reprod Med*. 2018; 36:143-51.

60. Cozzolino M, Coccia ME, Lazzeri G, et al. Variables Associated with Endometriosis-related Pain: A Pilot Study using a Visual Analogue Scale. *Rev Bras Ginecol Obstet*. 2019; 41:170-5.

61. Seyhan A, Ata B, Uncu G. The Impact of Endometriosis and Its Treatment on Ovarian Reserve. *Semin Reprod Med*. 2015; 33:422-8.

62. Muzii L, Miller CE. The singer, not the song. *J Minim Invasive Gynecol*. 2011; 18:666-7.

63. Collin V, Schaub M, Faller E, et al. Preserving Fertility by Treating the 3 Compartments: Laparoscopic Approach to Deep Infiltrating Endometriosis. *J Minim Invasive Gynecol*. 2018.

64. Dan H, Limin F. Laparoscopic ovarian cystectomy versus fenestration/coagulation or laser vaporization for the treatment of endometriomas: a meta-analysis of randomized controlled trials. *Gynecol Obstet Invest*. 2013; 76:75-82.

65. Hart RJ, Hickey M, Maouris P, et al. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database Syst Rev*. 2008; (2):CD004992. doi:CD004992.

66. Muzii L, Bellati F, Bianchi A, et al. Laparoscopic stripping of endometriomas: a randomized trial on different surgical techniques. Part II: pathological results. *Hum Reprod*. 2005; 20:1987-92.

67. Zhang CH, Wu L, Li PQ. Clinical study of the impact on ovarian reserve by different hemostasis methods in laparoscopic cystectomy for ovarian endometrioma. *Taiwan J Obstet Gynecol*. 2016; 55:507-11.

68. Ferrero S, Venturini PL, Gillott DJ, et al. Hemostasis by bipolar coagulation versus suture after surgical stripping of bilateral ovarian endometriomas: a randomized controlled trial. *J Minim Invasive Gynecol*. 2012; 19:722-30.

69. Chung JP, Law TSM, Chung CHS, et al. Impact of Haemostatic Sealant versus Electrocoagulation on Ovarian Reserve After Laparoscopic Ovarian Cystectomy of Ovarian Endometriomas: a Randomised Controlled Trial. *BJOG*. 2019.

70. Ata B, Turkgeldi E, Seyhan A, et al. Effect of hemostatic method on ovarian reserve following laparoscopic endometrioma excision; comparison of suture,

hemostatic sealant, and bipolar dessication. A systematic review and meta-analysis. *J Minim Invasive Gynecol*. 2015; 22:363-72.

71. Decleer W, Osmanagaoglu K, Verschueren K, et al. RCT to evaluate the influence of adjuvant medical treatment of peritoneal endometriosis on the outcome of IVF. *Hum Reprod*. 2016; 31:2017-23.

72. Garcia-Velasco JA, Domingo J, Cobo A, et al. Five years' experience using oocyte vitrification to preserve fertility for medical and nonmedical indications. *Fertil Steril*. 2013; 99:1994-9.

73. Rienzi L, Gracia C, Maggiulli R, et al. Oocyte, embryo and blastocyst cryopreservation in ART: systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance. *Hum Reprod Update*. 2017; 23:139-55.

74. Cobo A, Diaz C. Clinical application of oocyte vitrification: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril*. 2011; 96:277-85.

75. Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013; 31:2500-10.

76. Rienzi L, Romano S, Albricci L, et al. Embryo development of fresh 'versus' vitrified metaphase II oocytes after ICSI: a prospective randomized sibling-oocyte study. *Hum Reprod*. 2010; 25:66-73.

77. Goldman RH, Racowsky C, Farland LV, et al. Predicting the likelihood of live birth for elective oocyte cryopreservation: a counseling tool for physicians and patients. *Hum Reprod*. 2017; 32:853-9.

78. Cil AP, Bang H, Oktay K. Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis. *Fertil Steril*. 2013; 100:9.e3.

79. Elizur SE, Chian R, Holzer HEG, et al. Cryopreservation of oocytes in a young woman with severe and symptomatic endometriosis: a new indication for fertility preservation. *Fertil Steril*. 2009; 91:3.

80. Raad J, Sonigo C, Tran C, et al. Oocyte vitrification for preserving fertility in patients with endometriosis: first observational cohort study… and many unresolved questions. Letter to the Editor. *Eur J Obstet Gynecol Reprod Biol*. 2018; 220:140-1.

81. Somigliana E, Berlanda N, Benaglia L, et al. Surgical excision of endometriomas and ovarian reserve: a systematic review on serum antimüllerian hormone level modifications. *Fertil Steril*. 2012; 98:1531-8.

82. Coccia ME, Rizzello F, Barone S, et al. Is there a critical endometrioma size associated with reduced ovarian responsiveness in assisted reproduction techniques?. *Reprod Biomed Online*. 2014; 29:259-66.

83. Esinler I, Bozdag G, Arikan I, et al. Endometrioma . *Gynecol Obstet Invest*. 2012; 74:261-4.

84. Wu CQ, Albert A, Alfaraj S, et al. Live Birth Rate after Surgical and Expectant Management of Endometriomas after In Vitro Fertilization: A Systematic Review, Meta-Analysis, and Critical Appraisal of Current Guidelines and Previous Meta-Analyses. *J Minim Invasive Gynecol*. 2019; 26:311.e3.

85. D'Hooghe TM, Denys B, Spiessens C, et al. Is the endometriosis recurrence rate increased after ovarian hyperstimulation?. *Fertil Steril*. 2006; 86:283-90.

86. Benaglia L, Somigliana E, Vercellini P, et al. The impact of IVF procedures on endometriosis recurrence. *Eur J Obstet Gynecol Reprod Biol*. 2010; 148:49-52.

87. Coccia ME, Rizzello F, Gianfranco S. Does controlled ovarian hyperstimulation in women with a history of endometriosis influence recurrence rate?. *J Womens Health (Larchmt)*. 2010; 19:2063-9.

88. Sofiyeva N, Siepmann T, Barlinn K, et al. Gonadotropin-Releasing Hormone Analogs for Gonadal Protection During Gonadotoxic Chemotherapy: A Systematic Review and Meta-Analysis. *Reprod Sci*. 2018:1933719118799203.

89. Senra JC, Roque M, Talim MCT, et al. Gonadotropin-releasing hormone agonists for ovarian protection during cancer chemotherapy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2018; 51:77-86.

90. Hickman LC, Llarena NC, Valentine LN, et al. Preservation of gonadal function in women undergoing chemotherapy: a systematic review and meta-analysis of the potential role for gonadotropin-releasing hormone agonists. *J Assist Reprod Genet*. 2018; 35:571-81.

91. Yang XH, Ji F, AiLi A, et al. Effects of laparoscopic ovarian endometriosis cystectomy combined with postoperative GnRH-a therapy on ovarian reserve, pregnancy, and outcome recurrence. *Clin Exp Obstet Gynecol*. 2014; 41:272-5.

92. Chen X, Liu HY, Lang JH, et al. Effect of gonadotropin-releasing hormone agonist used before surgery on natural pregnancy rates in patients with ovarian endometriomas. *Zhonghua Fu Chan Ke Za Zhi*. 2018; 53:683-8.

93. Donnez J, Dolmans MM, Pellicer A, et al. Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation. *Fertil Steril*. 2013; 99:1503-13.

94. Donnez J, Squifflet J, Dolmans MM, et al. Orthotopic transplantation of fresh ovarian cortex: a report of two cases. *Fertil Steril*. 2005; 84:1018.

95. Jadoul P, Dolmans MM, Donnez J. Fertility preservation in girls during childhood: is it feasible, efficient and safe and to whom should it be proposed?. *Hum Reprod Update*. 2010; 16:617-30.

96. Meirow D, Ra'anani H, Shapira M, et al. Transplantations of frozen-thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria. *Fertil Steril*. 2016; 106:467-74.

97. Donnez J, Dolmans MM. Fertility preservation in women. *Nat Rev Endocrinol*. 2013; 9:735-49.

98. Stern CJ, Gook D, Hale LG, et al. First reported clinical pregnancy following heterotopic grafting of cryopreserved ovarian tissue in a woman after a bilateral oophorectomy. *Hum Reprod*. 2013; 28:2996-9.

99. Rodriguez-Wallberg KA, Oktay K. Recent advances in oocyte and ovarian tissue cryopreservation and transplantation. *Best Pract Res Clin Obstet Gynaecol*. 2012; 26:391-405.

100. Oktay K, Buyuk E, Rosenwaks Z, et al. A technique for transplantation of ovarian cortical strips to the forearm. *Fertil Steril*. 2003; 80:193-8.

101. Gosden RG. Low temperature storage and grafting of human ovarian tissue. *Mol Cell Endocrinol*. 2000; 163:125-9.

102. Liu J, Van der Elst J, Van den Broecke R, et al. Early massive follicle loss and apoptosis in heterotopically grafted newborn mouse ovaries. *Hum Reprod*. 2002; 17:605-11.

103. Donnez J, Dolmans MM, Demylle D, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. *Lancet*. 2022; 364:1405-10.

104. Van der Ven H, Liebenthron J, Beckmann M, et al. Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and delivery rates. *Hum Reprod*. 2016; 31:2031-41.

105. Donnez J, Dolmans MM, Diaz C, et al. Ovarian cortex transplantation: time to move on from experimental studies to open clinical application. *Fertil Steril*. 2015; 104:1097-8.

106. Practice Committee of American Society for Reproductive Medicine. Ovarian tissue cryopreservation: a committee opinion. *Fertil Steril*. 2014; 101:1237-43.

107. Oktay K, Harvey BE, Partridge AH, et al. Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2018; 36:1994-2001.

108. Martinez F. Update on fertility preservation from the Barcelona International Society for Fertility Preservation-ESHRE-ASRM 2015 expert meeting: indications, results and future perspectives. *Hum Reprod*. 2017; 32:1802-11.

109. Peccatori FA, Azim HA, Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013; 24 Suppl 6:70.

110. Dittrich R, Lotz L, Mueller A, et al. Oncofertility: combination of ovarian stimulation with subsequent ovarian tissue extraction on the day of oocyte retrieval. *Reprod Biol Endocrinol*. 2013; 11:19.

111. Dolmans MM, Marotta ML, Pirard C, et al. Ovarian tissue cryopreservation followed by controlled ovarian stimulation and pick-up of mature oocytes does not impair the number or quality of retrieved oocytes. *J Ovarian Res*. 2014; 7:8.

112. Kniazeva E, Hardy AN, Boukaidi SA, et al. Primordial Follicle Transplantation within Designer Biomaterial Grafts Produce Live Births in a Mouse Infertility Model. *Sci Rep*. 2015; 5:17709.

113. Oktay K, Nugent D, Newton H, et al. Isolation and characterization of primordial follicles from fresh and cryopreserved human ovarian tissue. *Fertil Steril*. 1997; 67:481-6.

114. Chiti MC, Dolmans MM, Hobeika M, et al. A modified and tailored human follicle isolation procedure improves follicle recovery and survival. *J Ovarian Res*. 2017; 10:8.

115. Chiti MC, Dolmans MM, Mortiaux L, et al. A novel fibrin-based artificial ovary prototype resembling human ovarian tissue in terms of architecture and rigidity. *J Assist Reprod Genet*. 2018; 35:41-8.

116. Oktay K, Oktem O. Ovarian cryopreservation and transplantation for fertility preservation for medical indications: report of an ongoing experience. *Fertil Steril*. 2010; 93:762-8.

117. Schubert B, Canis M, Darcha C, et al. Human ovarian tissue from cortex surrounding benign cysts: a model to study ovarian tissue cryopreservation. *Hum Reprod*. 2005; 20:1786-92.

118. Vitonis AF, Vincent K, Rahmioglu N, et al. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: II.

Clinical and covariate phenotype data collection in endometriosis research. *Fertil Steril*. 2014; 102:1223-32.

119. Garavaglia E, Sala C, Taccagni G, et al. Fertility Preservation in Endometriosis Patients: Anti-Müllerian Hormone Is a Reliable Marker of the Ovarian Follicle Density. *Front Surg*. 2017; 4:40.

120. Kuroda K, Ikemoto Y, Ochiai A, et al. Combination Treatment of Preoperative Embryo Cryopreservation and Endoscopic Surgery (Surgery-ART Hybrid Therapy) in Infertile Women with Diminished Ovarian Reserve and Uterine Myomas or Ovarian Endometriomas. *J Minim Invasive Gynecol*. 2019.

Tables and Figures

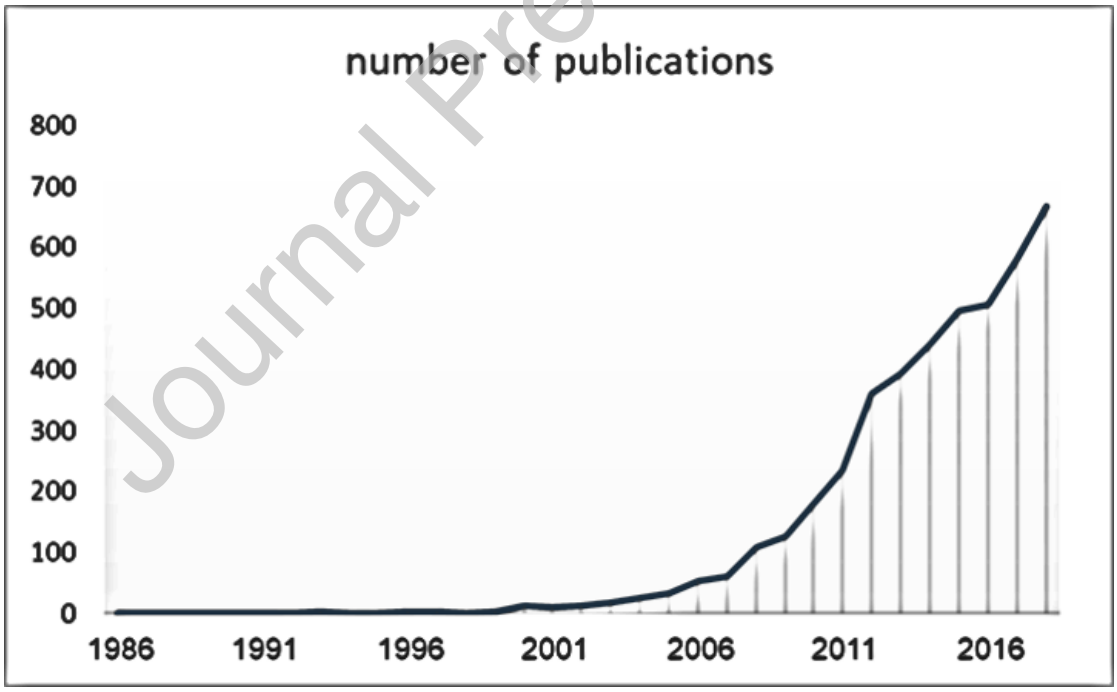

Figure 1

Number of publication per year on fertility preservation acording to a medline search using the term “fertility preservation” [MeSH Terms] OR “fertility preservation”

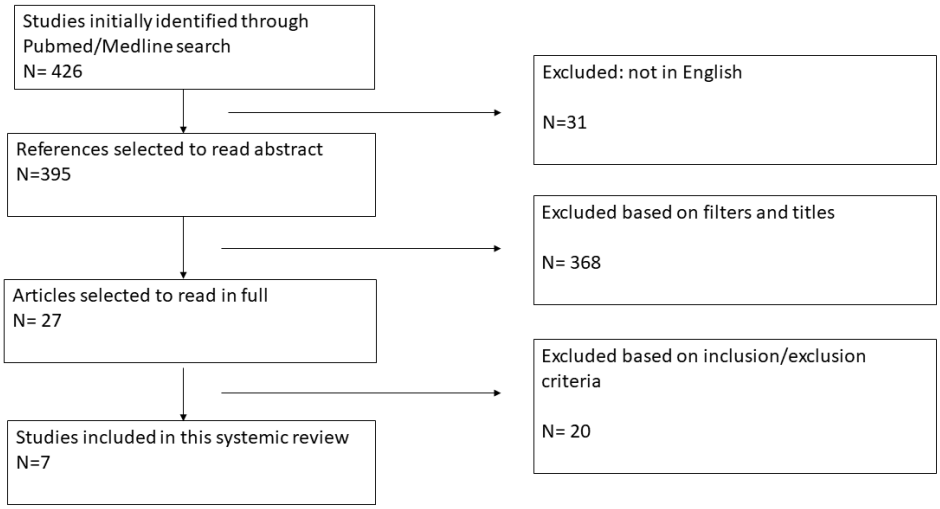

Figure 2

Flow diagram of systemic search of literature

Table 1

Original research on fertility preservation in endometriosis patients

OTCP – Ovarian Tissue Cryopreservation; AFC- Antral Follicle Count; AMH – Anti Mullerian Hormone, ART – Assisted Reproductive Technology

Study	Study design	Study aim	Inclusion criteria	Results	Limitations
Garavaglia E et al. 2017 (119)	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.	Two different AMH assays used. Insufficient power.
Raad J et al.2018 (80)	Retrospective cohort study	To describe a historic cohort of endometriosis patients having undergone oocyte cryopreservation	49 women suffering from 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, $p < 0.01$) Mean mature oocytes recovered: Endometrioma excision vs no excision (8.3 +5.2 vs. 5.3±3.7, $p < 0.01$)	No healthy controls. No report of pregnancy outcomes or risks.
Garcia-Velasco JA et al. 2013(72)	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 K et al. 2019 (120)	Retrospective cohort study	To determine predictive factors for clinical outcomes of surgery - ART hybrid therapy in infertile women with DOR with uterine fibroids and/or ovarian endometriomas	39 women with DOR (AMH<1.0 and/or advanced age >40) requiring surgery for uterine myomas and/or endometriomas.	14/39 (35.9%) women achieved a livebirth with surgery ART/hybrid therapy. Women achieving a live birth were significantly younger (median age 40 years (interquartile range [IQR], 38–41 years) vs 41.5 years (IQR, 41–42 years); p = 0.032) 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 SE et al. 2009 (79)	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 three cycles of ovarian stimulation, 21 oocytes were cryopreserved	Single case. No report of pregnancy outcomes or risks.
Donnez J et al. 2005 (94)	Case report	To asses survival of primordial follicles in OTCP and reimplantation in endometriosis patients	2 patients with severe endometriosis undergoing oophorectomy for recurrent endometriosis	Three months after reimplantation: Viable primordial follicles present and neovascular capillary network present	Single case. No report of pregnancy outcomes or risks.
Schubert B et al.2005 (117)	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/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)