



Is there an Indication for Fertility Preservation in Infertile Women with Endometriosis? How-Why-When?

Angelos Daniilidis¹, Panagiotis Papandreou^{1,2*}, Maurizio ND'Alterio³, Anastasia Vatopoulou¹ and Stefano Angioni³

¹2nd Department of Obstetrics and Gynecology, Hippokraton Hospital, Aristotle University of Thessaloniki, Greece

²Genesis Obstetrics and Gynecology Hospital, Greece

³Department of Surgical Sciences, Division of Gynecology and Obstetrics, University of Cagliari, Italy

Abstract

Women with endometriosis are at risk of compromised ovarian reserve because of the pathogenesis of their disease but also due to the iatrogenic negative contribution of a surgical treatment. Fertility preservation in women with endometriosis is a real issue and should be taken under concern especially in cases of women with age >35, with low ovarian reserve, bilateral endometriomas, recurrent surgical interventions, or even for all women with stage III and IV of disease. From February 2020 to August 2020 the authors systematically reviewed relevant literature that evaluates the possible benefits of fertility preservation in women with endometriosis. 68 articles were screened and 20 articles were finally included in our study. During the last decade oocyte vitrification, has permitted indeed major advances in the field of assisted reproductive technology. Cryopreservation of oocytes is the consolidated fertility preservation technique providing long term autonomy to women affected by endometriosis giving them a valid treatment option to enhance their reproductive chances. Specific robust data on fertility preservation in women with endometriosis, consensus on the strategy to adopt and cost-effectiveness studies are still lacking in the literature. The need of individualized approach taking into account age, ovarian reserve prior and planned surgical interventions is more than obvious. Counseling regarding fertility preservation by oocyte vitrification could be a first line approach for infertile women suffering from endometriosis.

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*Correspondence:

Panagiotis Papandreou, 2nd

Department of Obstetrics and Gynecology, Hippokraton Hospital, Aristotle University of Thessaloniki, Konstantinoupoleos Street 49, 54642, Thessaloniki, Greece,
E-mail: panos1914pap@hotmail.com

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Keywords: Cryopreservation; Endometrioma; Infertility; Laparoscopy; Oocyte vitrification

Abbreviations

ART: Artificial Reproductive Technology; AMH: Anti-Mullerian Hormone; ESHRE: European Society on Human Reproduction; ESGE: European Society on Gynaecological Endoscopy; IVF: *In Vitro* Fertilization; ICSI: Intracytoplasmic Sperm Injection

Introduction

Surgical treatment of endometriosis is considered gold standard, however, there has been increasing concern about the possible detrimental effects of surgical intervention on ovarian reserve [1]. Women with endometriosis are at risk of compromised ovarian reserve because of the pathogenesis of their disease but also due to the iatrogenic negative contribution of surgical treatment. Proper consideration should be given to fertility preservation in this specific population of women. Optimizing fertility preservation starts with preventing iatrogenic injury by using the best available technique in the most experienced surgical hands. Cryopreservation of oocytes is the established fertility preservation technique providing long term autonomy to women affected by endometriosis giving them a valid treatment option to enhance their reproductive chances. Data regarding fertility preservation options, outcomes and cost-effectiveness of oocyte vitrification for women with endometriosis are still in developmental stages [2].

Furthermore, there are no recommendations regarding counseling for fertility preservation. Although, it is clear that an individualized approach should be adopted, taking into account age, ovarian reserve prior and planned surgical interventions.

The aim of this review is to provide evidence that counseling regarding fertility preservation by oocyte vitrification should be a first line approach for infertile women suffering from endometriosis.

Material and Methods

Papers written in English and published in PubMed during the last decade were used to format this review. From February 2020 to August 2020 the authors searched relevant literature that evaluates the possible benefits of fertility preservation in women with endometriosis using keywords such as cryopreservation, endometrioma, infertility, laparoscopy, oocyte vitrification. Data were extracted independently by the authors, who evaluated all the potentially eligible papers by reading the title and abstract. After an initial screening of the title and abstract of all articles, citations that deemed to be irrelevant were excluded. When it was not possible to assess the eligibility of the article by only reading title and abstract, the authors read the full text. Manual search of review articles and cross-references completed the search. Data presented exclusively as abstracts in national and international meetings were also excluded. This study was a literature review and patients were not involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study or dissemination of results. No Institutional Review Board approval was required, because only published identified data were analyzed. Authors received no specific funding for this work. This paper aims to increase awareness on the validity of using fertility preservation techniques in order to enhance the reproductive chances in infertile women with endometriosis.

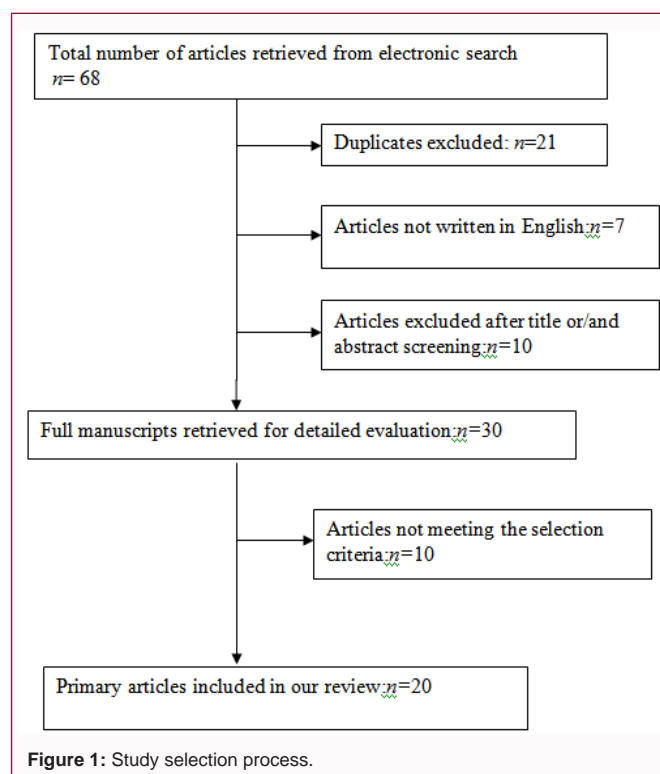
Results and Discussion

The search yielded 68 articles, all of which were available as free full text in PubMed. 21 of these were excluded as duplicates and 7 of these were excluded as not written in English. Another 10 articles were excluded, as it was clear from the title and abstract that they did not fulfill the selection criteria. We obtained full manuscripts of the remaining 30 articles and, following scrutiny of these, finally identified 20 relevant studies (Figure 1).

All of the studies investigated the validity of using fertility preservation techniques to enhance the reproductive chances in infertile women with endometriosis.

Surgical treatment for endometriosis and ovarian reserve

The mainstay of management for endometrioma, when treatment is required, is surgical treatment. Many studies have focused on the effectiveness of surgical treatment in improving the infertility of women with endometriosis [3]. The outcome of the aforementioned is highly dependent on the fact that precautions should be taken in the highest level before operating endometriomas [4]. Women of reproductive age who wish to conceive should undergo conservative surgical treatment in order to preserve the normal ovarian tissue and blood supply. European Society of Human Reproduction and Embryology (ESHRE) and European Society for Gynaecological Endoscopy (ESGE) guidelines extensively describe step by step approach on various aspects of fertility treatment of endometriosis [5,6]. Conservative surgical treatment options for ovarian endometriomas include ovarian cystectomy, laser ablation or plasma energy electrocoagulation. Specifically, excision of the cyst capsule, drainage of the cyst content and ablation by laser or plasma energy, drainage of the cyst content and electrocoagulation, combined technique (both excision of the cyst wall and ablation) and three step approaches, with three-month administration of Gonadotropin-Releasing-Hormone (GnRH) analogue between two laparoscopic surgeries, are the proposed surgical steps. These



methods are described in extensive detail but all have the potential to result in the iatrogenic compromise of ovarian reserve. Evidence for more conservative surgical techniques (that avoid the removal of the cyst wall such as laser vaporization) is still lacking. Even in the most experienced hands, surgery for ovarian endometriotic cysts leads to possible reduction of the ovarian reserve. Postoperatively, we observe lower levels of serum Anti-Mullerian Hormone (AMH), reduction of the antral follicle count on ultrasound, lower number of oocytes retrieved and greater risk for failure of controlled ovarian hyperstimulation during an assisted reproduction cycle [6-8].

Furthermore, the reduction of ovarian reserve may not be limited to the immediate post-operative period but unfortunately it seems that it might be progressive with time [9,10]. In such a diverse disease like endometriosis perhaps it should be more prudent to individualize our approach and treat according to the patients' needs. Minimal intervention and preservation of the healthy ovarian tissue is of highest priority. The Endometriosis Treatment Italian Club (ETIC) recommends that every effort should be made to prevent unnecessary procedures [1]. Experts do not suggest laparoscopy to detect and treat early-stage endometriosis just to treat fertility, removal of small ovarian endometriomas (diameter <4 cm) with the sole objective of improving the likelihood of conception, removal of uncomplicated deep endometriotic lesions in asymptomatic women, laparoscopy in adolescent women (<20 years) with suspicion of endometriosis. Obviously, removal of endometrioma by laparoscopy has actually a dual role on fertility treatment. On one hand it improves positively the chances for natural conception and on the other hand might reduce significantly the markers of ovarian reserve, thus diminish pregnancy rates even after Assisted Reproductive Technology (ART). Unfortunately, endometriosis is associated with a risk for recurrence rate after surgery between 11% to 50% within 1 to 5 years making future fertility capacity obscure. For younger women, when first surgery is performed, subsequent recurrence has higher odds with the

detrimental effects of a second operation, thus fertility preservation techniques are of utmost importance.

Effect of endometriosis on IVF/ICSI outcome

Recent literature is also pointing the other side of the story regarding the actual influence of endometriosis on the *In Vitro* Fertilization (IVF)/Intracytoplasmic Sperm Injection (ICSI) outcome [8,11,12]. In cases of minimal and mild endometriosis it is clearly demonstrated that surgery before ART is not going to improve fertility outcome [13]. Even for moderate and severe endometriosis the evidence does not support surgery before ART with regards to fertility outcomes [12,14]. A recent systematic review and meta-analysis [7] compared the results of the surgical treatment for endometrioma to no surgical intervention followed by assisted reproduction. Surgical management of endometrioma has actually no beneficial outcome on the following IVF/ ICSI. Results demonstrated no significant difference in rates of successful pregnancies [OR=0.88 (95% CI 0.60-1.29)] and clinical pregnancies [OR=1.08 (95% CI 0.80-1.45)] per assisted reproduction cycle, between women who underwent surgical treatment of endometriomas and those with no surgical treatment. The secondary outcomes showed no statistical difference in the number of oocytes retrieved [mean difference - 0.43 (95% CI -1.67, 0.80)], the total number of embryos created per cycle [mean difference 0.06 95% CI - 0.21-0.33], the gonadotropin ampoules used per cycle [mean difference 1.31 (95% CI -3.87, 6.50)] and the total gonadotropin dose per cycle [mean difference 244.81(95% CI - 525.43-1015.06)] between the two groups.

Fertility preservation for endometriosis - What options are available?

The discussion on fertility sparing before an operation for endometriosis is still in embryonic state, recommendations on oocyte banking is premature worldwide and the issue of fertility preservation is still debated. Still only a few publications are actually focusing and bringing to discussion the issue [15-17]. Of course, there is always the issue of cost effectiveness, as fertility preservation as an approach for all women who suffer from advanced stage of endometriosis, might compromise health systems. Efficacy data related to fertility preservation techniques in endometriosis patients are limited, and a cost-benefit analysis is required in relation also to the high incidence of the disease. In a large number of cases endometriosis equals to women with sub-optimal or low ovarian reserve who need several stimulations and oocyte retrievals. Repeated preservation cycles for oocyte accumulation can be costly and could potentially have in addition a physical or psychological impact. Oocyte retrieval performed in women with advanced endometriosis can be frequently challenging because of anatomical distortions, fixed ovarian cysts and adhesions. Especially for women who wish to conceive and suffer from endometriosis, predicting future fertility and the likelihood of requiring ART for conceiving is an undeniably hard task. We do have in our hands some tools to predict and validate the subgroup of these women who really have a compromised fecundity and offer them a reliable counseling are based on the laparoscopic findings, which has to be performed beforehand [18].

During the last decade oocyte vitrification, has permitted indeed major advances in the field of ART. Cryopreservation of oocytes is the established fertility preservation technique providing long term autonomy to women affected by endometriosis giving them a valid treatment option to enhance their reproductive chances. The effect of endometriosis on follicle/oocyte quality is an issue still under

investigation and there is still not a clear answer if a deleterious effect of the disease on vitrification, warming/thawing and reproductive outcome is a reality. A recent multicenter, observational study included 485 women with endometriosis whose oocytes were vitrified for future use [15]. The number of vitrified oocytes per cycle (6.2 ± 5.8) was higher for the non-surgical patients compared with the unilateral (5.0 ± 4.5) or bilateral (4.5 ± 4.4) surgery groups. As for the ovarian response authors concluded that vitrified oocytes (8.6 ± 6.9 vs. 5.1 ± 4.8) and Cumulative Live Birth Rate (CLBR) (72.5% vs. 52.8%) were higher in non-surgical patient versus the patients who previously had an operation. According to the conclusions, due to the detrimental effect of surgical excision of ovarian endometriomas in young women, fertility preservation offers a valid treatment option and performing surgery after ovarian stimulation for cryopreservation is suggested. Generally speaking, patients rarely receive a proper reproductive counseling at diagnosis of the disease. In most of the cases, fertility preservation is discussed only in advanced cases, in women who already have a reduced ovarian reserve or after a surgical intervention with a possible detrimental impact on fecundity. A Strengths, Weaknesses, Opportunities and Threats (SWOT) analysis tried to investigate possible factors that might be in favor or against in a project of decision making and strategic planning for fertility sparing in women with endometriosis [19]. According to authors specific strategies should be considered for the preservation of oocytes in women with endometriosis. Cryopreservation of oocytes in young women with a good ovarian reserve before the impact of age, endometriomas or endometrioma surgery should be seriously considered. Performing oocyte cryopreservation only in women at high risk of infertility, those with affected ovaries or with a reduced ovarian reserve leads to disappointing results since the oocyte yield is often poor requiring several stimulations. As for how many oocytes do, we need for achieving realistic chances of success it seems that there is no guarantee. Authors recommend the cryopreservation of 15 to 20 and 25 to 30 metaphase oocytes in women aged <38 or 38 to 40 years, respectively in order to give realistic chances to women to achieve one or more live-births [20].

Conclusion

Endometriosis imposes an individualized long-term treatment strategy that encompasses all aspects of the disease like pain relief, quality of life and fertility. Advances in stimulation protocols and adoption of oocyte vitrification have undoubtedly created new fields for preservation of fertility. Specific robust data on fertility preservation in women with endometriosis, consensus on the strategy to adopt and cost-effectiveness studies are still lacking in the literature. Fertility preservation in women with endometriosis is a real issue and should be taken under proper concern especially in cases of women with age >35, with low ovarian reserve, bilateral endometriomas, recurrent surgical interventions, or even for all women with stage III and IV of disease. Especially the later are going to undergo difficult and extensive laparoscopic operations for the treatment of pain, which might compromise even more their reduced fecundity. It is more than obvious that careful individualized selection of infertile women with endometriomas for surgical treatment prior to assisted reproduction should be appropriately designed according to patient personalized needs, as surgical treatment does not appear to increase the chances of successful pregnancy. This choice should be made after evaluating the potential benefit compared to the reduction of the ovarian reserve and the successful ovarian stimulation that any surgery causes. Proper counseling should address reproductive issues

from the first visit. But really after all this literature on hand regarding infertility due to endometriosis, compromise of ovarian reserve because of a “successful” operation, or even the reoperation rates, is there still a logical reason why the option of fertility preservation by ovarian stimulation and egg cryopreservation should not be a realistic option for women during counseling?

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