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Research Article

TREATMENT OF ENDOMETRIOSIS PRIOR TO ASSISTED FERTILIZATION CYCLES - SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background - Endometriosis is a gynecological disease characterized by the presence of endometrial tissue outside the uterine cavity. It is one of the leading causes of pelvic pain and female infertility. But, the effectiveness of endometriosis treatments prior to ART is not stablished until now.
Objectives - To know if medication and/or surgical treatments of endometriosis, prior to *in vitro* fertilization (IVF) in women with infertility, positively influence pregnancy rates.
Search Methods - We systematically reviewed randomized clinical trials with the following interventions: use of oral contraceptives, use of GnRH analogues, laparoscopy with endometrioma excision, laparoscopy with cauterization of endometriosis foci, and, finally, resection surgery of endometrioma followed by the use of GnRh. We found 5,834 articles in the following literature databases: Science Direct, Cochrane Controlled Trials Register (CCTR), Cochrane Database of Systematic Reviews (CDSR), EMBASE, Medline, PubMed and Reference lists.
Selection Criteria - We included randomized and non-randomized controlled trials that compared the results of IVF patients with endometriosis that had previously undergone treatment to those with no treatment (controls). It was compulsory for the groups to include: (1) a control group without treatment and one of the following: (2) a group that had previously undergone surgery; (3) a group that had undergone a prior medication treatment; (4) a group that had previously undergone medication and surgery treatment.
Data Collection and Analysis - Three authors (Bertoncelo, Gualberto and Millani) were responsible for the database research and were assigned to screen the titles and abstracts in order to discard studies that were clearly ineligible. Titles and abstracts were independently reviewed by two authors (Souza and Sanchez) to check for duplicates. Two authors (Silva and Bertoncelo) independently analyzed potential sources of bias according to the Cochrane Collaboration's Criteria as well as the validity of each study. A third reviewer (Faria Jr) checked the data and any disagreement was resolved by arbitration with a fourth author (Bartmann). We used meta-analysis softwares R Statistical software (version 3.02) with Metaphor and meta library to calculate odds ratio (OR), assess statistical heterogeneity between studies and determine meta-analysis outcomes.
Main Results - Of the 5,834 articles found in the databases, 2,871 were relevant, from which, 8 were selected for this review. A total of 1,199 women were included in the study.Clinical pregnancy rates were significantly higher in women who had laparoscopic surgery (OR 2.19, 95% CI 1.12 to 4.28), who used GnRHanalogues prior to IVF (OR 1.77, 95% CI 1.07 to 2.93) and oral contraceptives (OR 2.65, 95% CI 1.57 to 4.47).
Authors' Conclusions - To the results, treatments in order to remove endometriosis tumors do not improve pregnancy rates after IVF. The administration of GnRH agonist and oral contraceptives with or without laparoscopic surgery increases pregnancy rates. The same occurs with laparoscopic surgery alone. The increase in the number of pregnancies justifies their use before IVF treatments in patients with endometriosis.

INTRODUCTION

Background

Endometriosis is a common gynecological disease defined by the presence of ectopic endometrial tissue, with cellular activity, leading to peritoneal and ovarian implants (Biacchiardi *et al*., 2011). It is one of the main causes of pelvic pain and female infertility (van Loendersloot *et al*., 2014).

The prevalence of endometriosis is difficult to determine, since it depends on the population studied. However, data related to

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women in childbearing age show that the prevalence of endometriosis is of about 10 %, and the number rises to over 40 % among patients with symptoms such as dysmenorrhea and dyspareunia. In women with infertility, prevalence ranges from 20 % to 50%, and it is believed that endometriosis has a deleterious role in the fertility potential of such women (Navarro *et al*., 2006).

The relationship between endometriosis and infertility is well defined in the advanced stages of the disease, but we do not know what the relationship between minimal or mild endometriosis and infertility is, since many women with those stages of involvement do not present any reproductive difficulty (Canis *et al*., 1997.)

The causes of infertility are associated with ovulatory abnormalities and distorted pelvic anatomy (Barri *et al*., 2010). Endometriomas are most often removed, in order to improve spontaneous fertility or the outcome of AR treatments. Laparoscopy is the most frequently used surgical technique for endometrioma excision. In addition to reducing the disease and improving endometriosis symptoms, surgery also is believed to increase the chances of spontaneous pregnancy (Biacchiardi *et al*., 2010.) On the other hand, however, laparoscopy can also decrease ovarian responsiveness to stimulation, affecting the success of IVF (Matalliotakis *et al*., 2007). This may happen due to surgical trauma, that is, the removal of a healthy part of the ovarian tissue along with the endometrioma wall (Vercellini *et al*., 2011).

The best choice for an endometriosis treatment related to assisted reproduction techniques is still unknown. Some authors argue that the suppression of ovarian function, with hormone treatment only, prior to ovarian stimulation or not, would not improve pregnancy rates (Maria*et al*., 2010).

The ESHRE Committee on Endometriosis recommends surgery for the excision of endometriosis foci followed by IVF for patients with more advanced stages of pelvic endometriosis (stages III or IV) (Dunselman *et al*, 2014). Still, this recommendation is based on observational studies rather than randomized clinical trials.

Laparoscopic removal of endometriomas before IVF treatment, in order to improve results, is very common in clinical practice. Studies about the influence of surgically removing endometriomas on the outcome of IVF show that operated patients had comparable results to women without previous surgical intervention. However, some researchers argue that surgical interventions can affect ovarian reserves (Bongioanni *et al*., 2011). Moreover, some studies demonstrate that endometriomas with an average diameter of less than 4 cm must not be removed before AR procedures (Papathanasiou & Bhattacharya, 2015).

Objectives

In this study, we reviewed clinical trials on the impact of surgical and/or medication treatments of endometriosis on the outcome of ART.

METHODS

This study was structured according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA) and was prospectively registered in PROSPERO, International Prospective register of systematic reviews.

Criteria for considering studies for this review

Types of study

We included randomized and non-randomized controlled trials that compared the results of IVF patients with endometriosis that had previously undergone treatment to those with no treatment (controls).

Participants

It was compulsory for the groups to include: (1) a control group without treatment and one of the following: (2) a group that had previously undergone surgery; (3) a group that had undergone a prior medication treatment; (4) a group that had previously undergone medication and surgery treatment.

Interventions

The surgical interventions studied were: 1) open surgery for unilateral endometrioma excision; 2) open surgery for bilateral endometrioma excision; 3) laparoscopy for unilateral endometrioma excision; 4) laparoscopy for bilateral endometrioma excision; 5) diagnostic laparoscopy with the cauterization of pelvic endometriosis foci and, 6) endometrioma aspiration. The clinical interventions studied were: 1) use of GnRH analogues; 2) use of isolated progestogens and, 3) use of combined oral contraceptives.The outcome measurements studied were: 1) implantation rate; 2) clinical pregnancy rate.

Search strategy

We considered eligible for this review all studies (in any language) of randomized and non-randomized controlled trials that compared the results of IVF patients with endometriosis that had previously undergone treatment to those with no treatment (controls). It was compulsory for the groups to include: 1) a control group without treatment and one of the following: 2) a group that had previously undergone surgery; 3) a group that had undergone a prior medication treatment; 4) a group that had previously undergone medication and surgery treatment. Retrospective studies or studies that did not include the aforementioned groups were considered ineligible. There was no limitation as to the language or the population studied.

Assessment of Relevant Studies

5,834 scientific articles were researched with the following terms: (endometrioses) AND (endometrioma) AND (GnRH-a) AND (progesterone) AND (oral contraceptive) AND (surgery) AND (laparoscopy) AND (*in vitro* fertilization) OR (IVF) OR (Intracytoplasmic Sperm Injection) OR (ICIS) OR (embryo transfer) OR (assisted reproductive technology) OR (ET) AND (outcome) AND (pregnancy rates) AND (trial) OR (random). All the terms were adjusted according to the databases. Additionally, we manually included trials and systematic reviews of the reference lists.

Titles and abstracts were independently reviewed by two authors (Souza and Sanchez) to check for duplicates. The same authors assessed the studies eligibility and the presence of previous criteria for inclusion.

First, we selected articles, which fulfilled and met the eligibility criteria of the study. Then, we analyzed their data and set up charts and graphs to illustrate their outcomes.

Data items

Characteristics of the studies: authors, country, institution, funding sources, conflicts of interest, ethics approval, study design, time of the study, inclusion and exclusion criteria, number of participants in each group were assessed.

Outcomes

Primary outcome: clinical pregnancy
Secondary outcome: implantation rate per randomized woman

Data collection and analysis

Missing data: we tried to contact the authors of the studies in order to obtain missing data. The studies for which we were not able to obtain missing data were considered high-risk for attribution bias and were excluded.

Risk of bias: Two authors independently analyzed the risk of selection bias, performance (error in blinding of participants), detection (error in blinding of outcome), attrition (incomplete outcome data) and reporting bias (description of desired data only). Other potential sources of bias were also analyzed according to the Cochrane Collaboration's Criteria (Higgins et al., 2011).Due to the difficulty in detecting and correcting publication bias, the authors sought to minimize its impact by ensuring a comprehensive search for eligible studies and by remaining alert for any kind of duplicate data. We did not use funnel plot to explore the possibility of a smaller study (i.e., a tendency for estimates of the intervention effect to be more beneficial in smaller studies), because such analysis is useful only when at least ten studies are included.

To assessthe quality level evidence of each study we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE system). As all studies were RCTs, we started scoring as “high level of evidence”. Nevertheless, we downgraded the score when population was small and confidence interval was wide or contained the number 1.

Summary of measurements: The effects of clinical interventions or surgery were summarized as a reason for risk, since the outcome is dichotomous (pregnancy and no pregnancy). As a comparison, we used the difference in arithmetic means for studies in which there was also the assessment of number of oocytes retrieved, for example, we considered clinically relevant those comparisons within a confidence interval of 95 %.

We used meta-analysis softwares R Statistical software (version 3.02) with Metaphor and meta library for all the meta-analysis outcomes, and for the forest plot. Data from preliminary studies were combined by comparing various interventions versus no intervention or a different intervention. Favored pregnancy is shown to the right of the axis and non-favored pregnancy to the left, in the forest plot.

Since the studies included used different comparisons, we stratified the outcomes, separating the studies according to the interventions used to increase the chance of pregnancy: 1) ACO medication versus no treatment or placebo, 2) GnRH analogue versus no treatment or placebo OR GnRH analogue after surgery versus surgery alone (control), 3) endometrioma surgery versus no treatment, 4) laparoscopic surgery versus no treatment.

RESULTS

Study Selection

The electronic research was held in the months of August and October 2017 and a total of 5,834 articles were found. We excluded 3,136 articles after reading their titles and abstracts because they did not meet the eligibility criteria. Of the remaining 2,871, we selected only 30 articles as pertinent to the subject in the second round of assessment by the authors. Of those selected, 6 were review articles (Kolibianakis et al., 2006; Ozkan *et al.*, 2008; Macer and Taylor, 2012; Giudice, 2010; Senapati and Barnhart, 2011; van Loendersloot et al., 2014;), 4 were meta-analysis articles (Hart *et al.*, 2005; Sallam *et al.*, 2006; Jin & Beguerie, 2014; Gupta *et al.*, 2006;), 4 were retrospective articles (Littman et al., 2005; Donnez et al., 2001; Geber et al., 2002; Barri *et al.*, 2010), 3 addressed endometriosis treatments, but with no relation to IVF (Soares *et al.*, 2012; Parazzini, 1999; Darai *et al.*, 2011;), 2 had ovarian reserve evaluation as an outcome, not pregnancy (Tsolakidis *et al.*, 2010; Biacchiardi *et al.*, 2011;), 2 were guidelines (Kennedy *et al.*, 2005; Cook *et al.*, 1995;), 2 were case control studies (Shawki, 2012; Aboulghar *et al.*, 2002;)The 8 articles used in this meta-analysis fulfilled the eligibility criteria (Dicker *et al.,* 1992; Bianchi *et al.*, 2009; Surrey *et al.*, 2002.; Demirol *et al.*, 2006; Pabuccu *et al.*, 2004; Somigliana *et al.*; 2008; De Ziegler., 2010; Decleer *et al.,* 2016)(Figure 1 and Table 1).

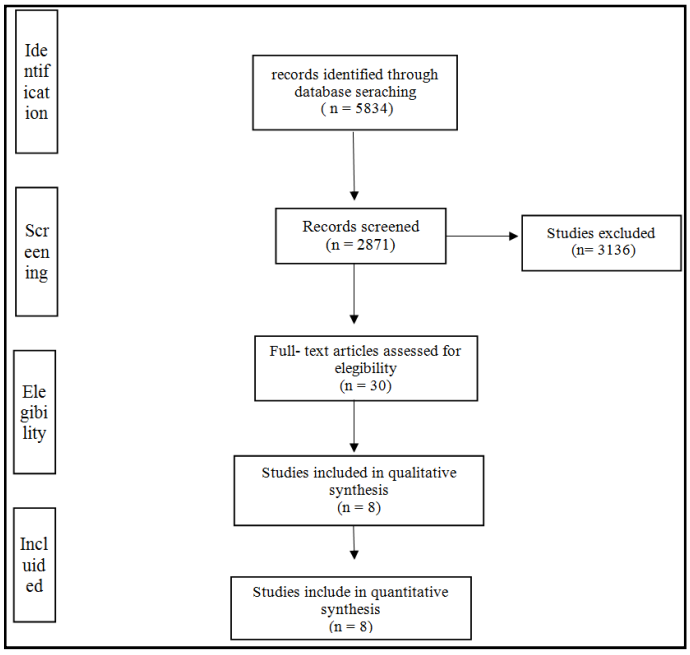


Figure 1 steps of meta-analysis composition

Characteristic of the studies

The studies used were clinical trials. A clinical trial is the preferred procedure in therapeutic experiments, often used to test the effectiveness of a given treatment approach in a population of patients, or to collect information about the side effects of a given treatment.

Table 1 characteristics of the studies included

Characteristics of included studies	Somigliana	Demirol	Pabuccu	Bianchi	Surrey	Dicker	Decleer	Ziegler
Year	2008	2006	2014	2009	2002	1992	2016	2010
Country	Italy	Turky	Turky	Brazil	USA	Israel	Belgium	France
Funding sources	Not described	Not described	Not described	Not described	Not described	Not described	Not described	Not described
Conflict of interest	Not described	Not described	Not described	Not described	Not described	Not described	Not described	Not described
Ethic Approval	Not described	Not described	Yes	Not described	Not described	Not described	Not described	Not described
Writen Consent	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study Design	Prospective, randomized	Prospective, randomized	Prospective, randomized	Propective non-randomized with intervention	Prospective, randomized	Randomized	Prospective, randomized	Prospective, randomized
Inclusion criteria	1) Previous laparotomic and/ or laparoscopic enucleation of bilateral ovarian endometriomas 2) availability of detaileddescripition of the surgycal intervention 3) Histopatologic confirmed diagnosis of endometriomas and 4) age < 40 years at the time of IVF/ICSI.	1) Patients with endometriomas> = 3 cm and < 6 cm who were referred to ICSI 2) Patients with single or multiple unilateral ovarian endometriomas with diameter between 3 and 6 cm.	1) Aspiration of endometrioma at the beginning of the ovarian stimulation 2) nonaspirated endometriomas 3)history of endometrioma surgery 4) tubal factor inferlitity 5) normal uterine cavity.	1) clinical and ultrasound evidence of deep infiltrative endometriosis. 2)Age between 21 and 38 years. 3) Indication for IVF 4) Presence of at least 1 functioning ovary. 5) normal uterine cavity 6) FSH < 15.	1) endometriosis documented at laparoscopy or laparotomy. 2) Regular menses 3) Candidates for IVF.	Women with severe degrees of endometriosis, who faleid to conceive and were referred to IVF..	Patients younger than 38 years with indication for IVF-treatment	1) Patients with endometriosis who were diagnosed either surgically or by ultrasound with images of single or multiple endometriomas.
Exclusion criteria	1) Previuos ovarian surgery for endometriomas in only one gonad 2) Previous ovarian surgery for non-endometriotic benign ovarian cysts and/ or ovarian malignancy 3) Previous mono/bilateral adnexectomy 4) Use of criostored spermatozoa 5) Previous IVF-cycle	1) Patients with multiple bilateral endometriomas with diameter between 3 and 6 cm.	1) Thaw cycles	1) Endocrinological disease. 2) Ejaculate with less than 1% normal spermatozoa.	1) Patients with early folicular phase serum FSH levels greater than 12 UM/ml and evidence of evarian endometrioma. 2) patients had received prolonged GnRH agonist therapy as treatment for endometriosis within 12 months.	1) Not reported	Patients older than 38 years, severe male problems,e.g.indication for testicular sperm extraction, severe endometriosis,ovarian endometriotic cysts, deep fibrosing endometriosis of the rectovaginal septum and uterine pathology such as congenital malformation of the uterine cavity or fibroids. Also patients with major endocrine problems were excluded.	1) Not reported
Groups	Group 1: patients underwent bilateral endometriomascystectomy prior to IVF/ICSI cycles. Group 2: patients underwent IVF/ICSI cycles directly	Group 1: patients underwent conservative laparoscopic ovarian surgery before ICSI. Group 2: patients underwent ICSI directly	Group 1: aspiration of endometriomas at the beginning of COH in patients with ovarian endometriomas and no history of previous surgery Group 2: nonaspirated endometriomas. Group 3: previous endometrioma surgery patients without ovarian endometriomas at the beginning of COH. Group 4 (Control): and tubal factor infertility	Group I: IVF/ICSI alone. Group II: IVF/ICSI with previous laparoscopic removal of endometriosis lesions	Group 1: Patients who received a depot preparation of GnRH agonist prior to IVF Group 2: Patients with standart ovarian stimulation for IVF.	Group A: regular ovarian stimulation for IVF. Group B: 6-months of hormonal suppression with a GnRH agonist before IVF	All patients were treated by laser surgery before intervention. Group A: 3-month pituitary suppression with a long-acting GnRH agonist before ovarian stimulation for IVF. Group B: IVF straight away, without hormonal treatment.	Group I: Patients received oral contraceptives before ART. Group II: received no oral contraceptive pretreatment.
Interventions	bilateral endometrioma surgery	laparoscopic endometrioma surgery (cystectomy)	endometrioma aspiration	laparoscopic removal of endometriotic lesions	3 months pretreatment with long-action GnRH agonist before IVF	6 months pretreatment with GnRH agonist before IVF	6 months pretreatment with GnRH agonist before IVF	Pretreatment with Oral Contraceptives before IVF
Principal Outcomes	Folicle number, retrieved oocytes, embryos obtained, pregnancy rate	fertilization rate, implantation rate, clinical pregnancy rate	mean fertilization rate, metaphase II oocytes, implantation rate, clinical pregnancy and spontaneous abortion	pregnancy rate, implantation rate, fertilization rate	ongoing pregnancy rate per cycle, implantation rate and implantation rate per embryo transfered.	fertilization rate, cleavage rate, number of transfers, pregnancy rate	number of MII oocytes obtained, embryo transfer, embryo quality, pregnancy rate	the number of oocytes, clinical pregnancy rate

Risks of bias inside the study

Although randomized clinical trials are the gold standard for the development of research with human subjects, this type of study is very prone to bias, whether because of the arbitrariness of the researchers in their sample selection and measurement of the variables analyzed, or because of the difficulty to control other factors that can influence the clinical outcome.

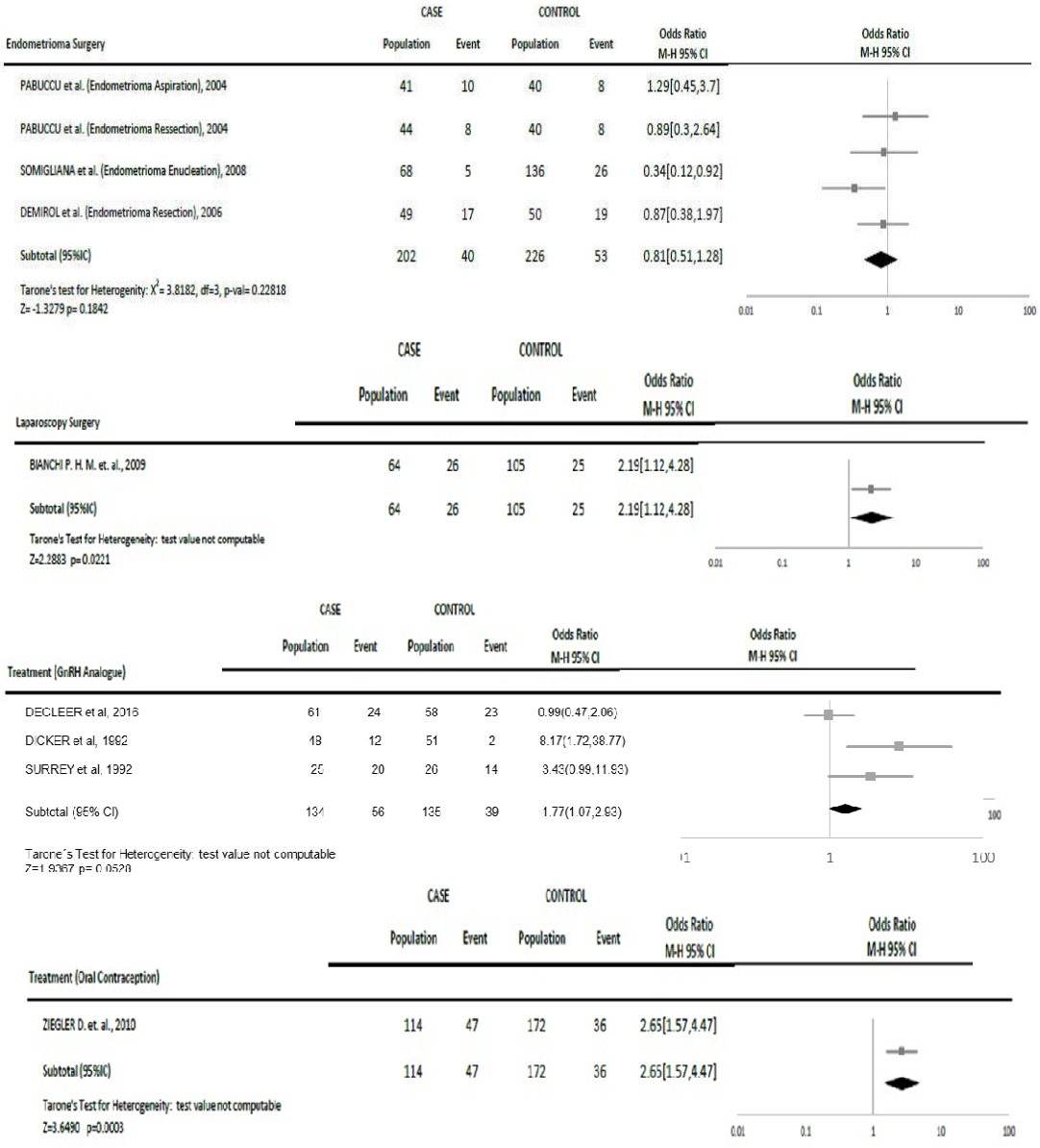
Outcome of individual studies

The outcomes of individual studies are presented in forest plot (Table 2)

Regarding laparoscopic surgery to remove lesions of endometriosis prior to IVF, there was one RCT including 169 patients in total (64 patients underwent surgery and 105 formed the control group). Respectively, 26 became pregnant in the treated group and 25 in the control group (OR 2.19, 95% CI 1.12 to 4.28). There was a statistical difference between the groups in favor of the group submitted to surgery.

In the 3 trials that evaluated treatment with GnRH analogs prior to IVF, 269 patients were included, 134 patients being submitted to previous treatment and 135 as a control group.

Table 2. Forest Plot patients with endometriosis/endometrioma, with interventions and clinical pregnancy rate outcome.



We evaluated 4 randomized clinical trials (RCTs) on endometrioma removal surgery, in which 428 patients were included: 202 patients underwent surgery (40 patients became pregnant), and 226 formed the control group (53 patients became pregnant) with OR 0.81, 95% CI 0.51 to 1.28. Based on these data, there was a reduction in pregnancy rate in patients undergoing endometrioma removal before IVF.

In these groups, 56 became pregnant in the first group and 39 in the second group (OR 1.77, 95% CI 1.07 to 2.93), which shows that there is a statistically significant increase in pregnancies in patients who used GnRH analogs prior to IVF.

The study that analyzed the use of oral contraceptives prior to IVF included 286 patients, 114 in the treated group and 172 in the control group. The groups had respectively 47 and 36

pregnancies (OR 2.65, 95% CI 1.57 to 4.47). This study also demonstrates statistical difference in favor of the group that used the medication.

determine the accuracy of the clinical pregnancy rate of one study that used GnRh analogue (Surrey), due to the lackof statistical data in the article.

Table 3 Quality Level Evidence of each study

Study	Intervention Type before IVF	Group	OD / CI	Population	Evidence Quality Level	Observation
PABUCCU et al, 2004	Endometrioma Aspiration And Ressection	Endometrioma Surgery	1.29(0.45,3.7) and 0.89(0.3,2.64)	125	Moderate	CI contains 1
SOMIGLIANA et al, 2008	Endometrioma Enucleation	Endometrioma Surgery	0.34(0.12,0.92)	204	High	
DEMIROL et al, 2006	Endometrioma Ressection	Endometrioma Surgery	0.87(0.38,1.97)	99	Moderate	CI contains 1
BIANCHI et al, 2009	Laparoscopy	Laparoscopic Surgery	2.19(1.12,4.28)	169	High	
DECLEER et al, 2016	Treatment with GnRH analogue	Treatment (GnRH analogue)	0.99(0.47,2.06)	166	Moderate	CI contains 1
DICKER et al, 1992	Treatment with GnRH analogue	Treatment (GnRH analogue)	8.17(1.72,38.77)	113	Moderate	Wide confidence interval
SURREY et al, 2002	Treatment with GnRH analogue	Treatment (GnRH analogue)	3.43(0.99,11.93)	51	Moderate	Low population number
ZIEGLER et al, 2010	Treatment with Oral Contraceptive	Treatment (Oral Contraception)	3.33(0.96,11.54)	286	Moderate	Good population number, but wide confidence interval

DISCUSSION

This article aimed to systematically assess the literature and to transparently and extensively review whether it is worth treating a patient's endometriosis before she undergoes Assisted Reproduction treatments. In practice, the treatment implies a delay of about 6 or more months in fertilization. In this review we seek to verify whether surgical and/or medication treatments warrant the delay in the treatment in terms of greater number of pregnancies.

A recent Cochrane review suggests that the administration of GnRH analogues in women with endometriosis for a period of three to six months prior to IVF increases the probability of clinical pregnancy fourfold (Sallam*et al*., 2006), and our work confirms such claim. Regarding Laparoscopic Surgery, we analyzed studies showing that laparoscopic resection or ablation in minimal or mild endometriosis increases fecundity in infertile women (Navarro*et al*., 2006), but according to the ESHRE Guideline for the Diagnosis and Treatment of Endometriosis, some studies' analysis of the data obtained were biased. In addition, the study showed no evidence that the fertility rate after surgical treatment was influenced by the ablation method used (electrosurgical or laser). Thus, literature does not have controlled randomized clinical studies or meta-analysis that have assessed if surgical removal improves pregnancy rates for moderate or severe endometriosis cases.

As for the limitations of this study, we emphasize the great heterogeneity of the samples and of the studies, in addition to the small amount of clinical trials. Of the 2,871 articles related to endometriosis and IVF, only 8 were suitable for meta-analysis. Regarding medication treatments, we found only one using oral contraceptives. One of the studies was not described as a clinical trial.However, after discussion, we considered the study interventionist and apt to be included in the sample. We tried to minimize these limitations with new searches and by contacting the authors.

In the group of studies that analyzed endometrioma surgery (Pabuccu; Somigliana; Demirol), we had to analyze the results of the first one (Pabuccu) separately for endometrioma aspiration and resection of endometrioma.It was difficult to

Despite the inherent limitations of any clinical study, we can conclude that it is valid to use GnRH analogues or oral contraceptives before AR treatments. Similarly, surgery for resection of endometriosis foci have shown increased chances of post-IVF pregnancy, in addition to reducing pelvic pain (Bedaiwy and Barker, 2012). The interventions that presented a negative effect were the resections of endometrioma, as stated earlier.

The cases treated with laparoscopy surgery for resection of endometriosis lesions and the cases that utilized oral contraceptives have pregnancy rates statistically different from their control groups. The patients that have been through these treatments have higher chances of getting pregnant than the ones on the control group. In the first case the rate is 2.19, which means that the chances of getting pregnant increase in 2.19 times while in the second case this chance gets to 2.65 times.

Highlights

In this systematic review and meta-analysis, we demonstrate that the use of medication and surgery for resection of endometriosis foci increases the chances of pregnancy after IVF. The resection of endometriomas demonstrates a negative effect.

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