JOURNAL OF OBSTETRICS AND GYNAECOLOGY
https://doi.org/10.1080/01443615.2021.1959536

ORIGINAL ARTICLE

Reproductive outcomes after laparoscopic surgery in infertile women affected by ovarian endometriomas, with or without *in vitro* fertilisation: results from the SAFE (surgery and ART for endometriomas) trial

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ABSTRACT

We performed a retrospective cohort study, namely "Surgery and ART for Endometriomas" (SAFE) trial (Clinical Trial ID: NCT03717870), including women who underwent laparoscopic cystectomy for endometrioma before first IVF and compared their reproductive outcomes with the ones of women without endometriosis and with unexplained infertility, tubal factor or male factor infertility. We found that women who underwent previous laparoscopic cystectomy for endometrioma had higher FSH and LH levels between the 2nd and 5th day of the cycle before IVF, required higher doses of gonadotrophins for ovarian stimulation and had a lower number of retrieved oocytes compared with other types of infertility. Nevertheless, pregnancy and delivery rates remain comparable to other causes of infertility. In addition, differences in ovarian stimulation parameters between endometriosis and other types of infertility lost significance with the increase of women's age. These pieces of information can be considered useful to make adequate counselling about reproductive outcomes for infertile women with ovarian endometriomas and allow a proper decision-making approach shared with the patient.

IMPACT STATEMENT

- **What is already known on this subject?** Although endometriomas are common findings in infertile women, whether they should be surgically removed before an *in vitro* fertilisation (IVF) is a long-lasting debate, and current evidence does not offer a robust background to draw firm recommendations.
- **What do the results of this study add?** Women who underwent previous laparoscopic cystectomy for endometrioma need higher doses of gonadotrophins for ovarian stimulation and have a lower number of retrieved oocytes, compared with other types of infertility. Pregnancy and delivery rates remain comparable to other causes of infertility.
- **What are the implications of these findings for clinical practice and/or further research?** These pieces of information can help to make adequate counselling about reproductive outcomes for infertile women with ovarian endometriomas and allow a proper decision-making approach shared with the patient.

KEYWORDS
Endometriosis; laparoscopic surgery; *in vitro* fertilisation; reproductive outcomes

Introduction

Endometriosis is a chronic inflammatory disease, characterised by the presence of endometrial-like tissue, gland and stroma outside from uterine cavity (Laganà et al. 1975; Greene et al. 2016). Women affected by endometriosis could experience symptoms such as dysmenorrhoea, dyspareunia, chronic pelvic pain and/or infertility, whereas other less frequent symptoms depend on the specific affected organs (Giudice 2010).

The incidence of endometriosis is estimated to be 10–15% in women of reproductive age, with a higher prevalence in those affected by infertility. In this subgroup of patients, the incidence of endometriosis is between 20 and 50% (Parazzini et al. 2017; Laganà and La Rosa 2020). About 30% of affected women have no symptoms, and endometriosis is found accidentally during a surgical intervention due to other indications (Viganò et al. 2004; Shafrir et al. 2018). Fertility rates may be reduced in women with endometriosis, potentially related to the severity of the disease (Lessey et al. 2018).

Although endometriomas are common findings in infertile women, whether they should be surgically removed before an *in vitro* fertilisation (IVF) is a long-lasting debate, and

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current evidence does not offer a robust background to draw firm recommendations. On the one hand, surgical enucleation of endometriomas may facilitate subsequent oocyte retrieval after ovarian stimulation, reducing the possibility of follicular fluid contamination or infection and the risk of chemical peritonitis, and allows histological diagnosis of occult malignancy. On the other hand, surgery exposes the patients to the risk of potential complications, even when performed with a minimally invasive approach, and may cause iatrogenic reduction of ovarian reserve and consequently decrease the success rate of assisted reproduction technology (ART) (Nickkho-Amiry et al. 2018; Šalamun et al. 2018). In addition, women with endometrioma experience a progressive decline in serum anti-Müllerian hormone (AMH) levels, which is faster than that in healthy women (Kasapoglu et al. 2018): considering this element, endometriomas *per se* have a detrimental role on the ovarian reserve, even without surgery.

To date, the results of the meta-analysis included in international guidelines lead to different recommendations about the decision to operate or not (Dunselman et al. 2014). Most of the available pieces of evidence suggest that surgical procedure causes a decrease of ovarian reserve; in addition, compared to women with other causes of infertility (Hamdan et al. 2015), the ones affected by endometriosis need higher doses of gonadotropins for ovarian stimulation, and have a lower number of retrieved oocytes and good quality embryos, although the pregnancy and delivery rates are comparable (Hirsch et al. 2018). Therefore, the decision about surgery should be individualised, based on endometrioma's size, presence of other symptoms besides infertility, such as chronic pelvic pain, dysmenorrhoea and dyspareunia, failed medical therapies to control the symptoms, previous failed ART, and patient's age and ovarian reserve.

Considering the lack of robust data about the topic, in this study we aimed to investigate reproductive outcomes in women who underwent laparoscopic enucleation of ovarian endometriomas, with subsequent IVF.

Materials and methods

Study design and inclusion criteria

In the setting in which the study was performed, after exclusion of male factor, infertile women are clinically evaluated and undergo diagnostic/operative laparoscopy, and additional hysteroscopy, if indicated. When surgical management does not allow natural conception within 6–12 months, patients are addressed to the IVF program.

Our retrospective cohort study, namely "Surgery and ART for Endometriomas" (SAFE) trial (Clinical Trial ID: NCT03717870), included patients (Group 1) who underwent laparoscopic cystectomy for endometrioma before first *in vitro* fertilisation and embryo transfer (IVF-ET). The data were retrieved from our medical records, including databases for surgical procedures and IVF database, between 1st January 2011 and 31st December 2016. The IVF outcomes of this group were compared with the ones of unexplained infertility (Group 2), male factor infertility (Group 3) and tubal factor infertility (Group 4). In groups, 2, 3, and 4 endometriosis were ruled out by ultrasound followed by laparoscopy and visual inspection of the pelvic cavity.

The results of each group were further stratified and compared with the other ones, based on the women's age: below 35 years, between 35 and 40 years and over 40 years.

Surgical procedure and IVF protocol

The surgical procedure consisted of stripping, bipolar coagulation only when necessary for hemostasis and, rarely, ovarian suture. Laparoscopies were performed by skilled senior surgeons, each one with more than 200 performed laparoscopic treatments for major gynecological surgery.

All the enrolled patients had a history of infertility of not less than 2 years. After the surgical procedure, they were followed for 0–12 months, depending on the status. In cases of deep infiltrating endometriosis or severe (stage III–IV) endometriosis with adhesions, we advised them to undergo IVF within 3 months, otherwise, in young patients, we waited up to 12 months for natural conception before addressing them to IVF.

The IVF-ET procedure were offered to the women who failed to conceive spontaneously from 6 to 12 months after laparoscopic surgery. Short antagonist cetrorelix protocol or long desensitisation buserelin protocol were used for ovarian stimulation, as previously described (Korosec et al. 2014). We used the blastocyst grading system proposed by Gardner et al. (Gardner et al. 2000). One or two embryos were transferred on day 3 or 5 after oocyte retrieval. IVF procedures were performed by skilled senior gynaecologists, with an experience in IVF of more than 5 years.

Main outcomes and statistical analysis

Main outcome measures were follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels between 2nd and 5th day of the cycle before IVF procedure, total gonadotrophin dose, number of oocytes retrieved, number of developed embryos, pregnancy rate per ET and delivery rate.

Continuous variables with a normal distribution were compared using *t*-test, whereas dichotomous variables using χ^2 analysis, between cases (Group 1) and control groups through post-hoc analysis. The mean differences and 95% confidence intervals (95% CI) were calculated with two-sided p values. The significance level was set at $p < .05$. Data were processed with the program IBM SPSS Statistics for Windows, Version 25.0 (IBM Corporation, Armonk, NY, USA).

Ethical and methodological standards

The design, analysis, interpretation of data, drafting and revisions conform to the Helsinki Declaration, the Committee on Publication Ethics (COPE) guidelines (http://publicationethics.org/), and the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) (Benchimol et al. 2015) statement, available through the EQUATOR (enhancing the quality and transparency of health research) network (www.

Table 1. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels between 2nd and 5th day of the cycle before *in vitro* fertilisation (IVF) procedure and total gonadotrophin dose used for ovarian stimulation in women who underwent laparoscopic cystectomy for endometrioma (Group 1), unexplained infertility (Group 2), male factor infertility (Group 3) and tubal factor infertility (Group 4), stratified for age.

	Group 1 (endometrioma)	Group 2 (unexplained infertility)	Group 3 (male factor infertility)	Group 4 (tubal factor infertility)	*p*
FSH					
All patients (*n* = 883)	7.72 ± 3.10 (*n* = 226)	6.90 ± 2.02 (*n* = 149)	6.93 ± 1.95 (*n* = 263)	6.60 ± 1.85 (*n* = 245)	G1 vs G2: <.01 G1 vs G3: <.01 G1 vs G4: <.01
<35 years (*n* = 543)	7.70 ± 3.44 (*n* = 151)	6.84 ± 2.12 (*n* = 91)	6.91 ± 1.90 (*n* = 159)	6.69 ± 1.85 (*n* = 142)	G1 vs G2: .02 G1 vs G3: .01 G1 vs G4: <.01
35–40 years (*n* = 305)	7.75 ± 2.32 (*n* = 71)	6.97 ± 1.86 (*n* = 55)	6.99 ± 1.86 (*n* = 85)	6.46 ± 1.82 (*n* = 94)	G1 vs G2: .04 G1 vs G3: .03 G1 vs G4: <.01
>40 years (*n* = 35)	7.67 ± 1.79 (*n* = 4)	7.61 ± 1.92 (*n* = 3)	6.89 ± 2.74 (*n* = 19)	6.80 ± 2.27 (*n* = 9)	G1 vs G2: .97 G1 vs G3: .59 G1 vs G4: .37
Average FSH per cycle (*n* = 1599)	7.82 ± 3.09 (*n* = 390)	6.72 ± 1.95 (*n* = 294)	7.00 ± 1.92 (*n* = 461)	6.57 ± 1.72 (*n* = 454)	G1 vs G2: <.01 G1 vs G3: <.01 G1 vs G4: <.01
LH					
All patients (*n* = 883)	5.42 ± 3.00 (*n* = 226)	4.79 ± 2.39 (*n* = 149)	4.83 ± 2.54 (*n* = 263)	4.64 ± 3.13 (*n* = 245)	G1 vs G2: .03 G1 vs G3: .02 G1 vs G4: .01
<35 years (*n* = 543)	5.29 ± 2.83 (*n* = 151)	4.65 ± 2.30 (*n* = 91)	4.98 ± 2.87 (*n* = 159)	4.70 ± 2.80 (*n* = 142)	G1 vs G2: .07 G1 vs G3: .55 G1 vs G4: .07
35–40 years (*n* = 305)	5.16 ± 1.07 (*n* = 71)	5.01 ± 2.59 (*n* = 55)	4.72 ± 1.94 (*n* = 85)	4.55 ± 3.67 (*n* = 94)	G1 vs G2: .36 G1 vs G3: .09 G1 vs G4: <.0001
>40 years (*n* = 35)	3.26 ± 0.70 (*n* = 4)	4.90 ± 1.10 (*n* = 3)	4.04 ± 1.91 (*n* = 19)	4.73 ± 1.78 (*n* = 9)	G1 vs G2: .06 G1 vs G3: .17 G1 vs G4: .20
Average LH per cycle (*n* = 1599)	5.51 ± 2.96 (*n* = 390)	4.62 ± 2.39 (*n* = 294)	4.80 ± 2.43 (*n* = 461)	4.64 ± 2.87 (*n* = 454)	G1 vs G2: <.01 G1 vs G3: <.01 G1 vs G4: <.01
Gonadotrophins used for ovarian stimulation					
All patients (*cycles*, *n* = 1599)	2162 ± 842 (*n* = 390)	1868 ± 706 (*n* = 294)	1798 ± 731 (*n* = 461)	1913 ± 779 (*n* = 454)	G1 vs G2: <.01 G1 vs G3: <.01 G1 vs G4: <.01
<35 years (*cycles*, *n* = 955)	2177 ± 885 (*n* = 270)	1804 ± 691 (*n* = 161)	1736 ± 606 (*n* = 278)	1821 ± 713 (*n* = 246)	G1 vs G2: <.01 G1 vs G3: <.01 G1 vs G4: <.01
35–40 years (*cycles*, *n* = 554)	2131 ± 757 (*n* = 112)	1882 ± 707 (*n* = 121)	2006 ± 703 (*n* = 144)	1998 ± 844 (*n* = 177)	G1 vs G2: .01 G1 vs G3: .14 G1 vs G4: .15
>40 years (*cycles*, *n* = 90)	2081 ± 376 (*n* = 8)	2567 ± 529 (*n* = 12)	2126 ± 797 (*n* = 39)	2154 ± 816 (*n* = 31)	G1 vs G2: .40 G1 vs G3: .71 G1 vs G4: .87

Data are expressed as means ± standard deviations.

equator-network.org). The study was approved by the National Medical Ethics Committee of Slovenia (Approval ID: 0120-174/2018/6). The data collection was anonymized, taking into account the observational nature of the study and standardised approaches for the usual management of the patients, without personal data that could lead to formal identification. Each patient enrolled in this study signed informed consent for all the procedures and to allow data collection and analysis for research purposes. The study was non-advertised, and no remuneration was offered to encourage patients to give consent.

Results

The study group (Group 1) included 256 women (393 cycles), the group with unexplained infertility (Group 2) included 180 women (295 cycles), the group of male-factor infertility included (Group 3) included 319 women (465 cycles), and group with the tubal factor of infertility (Group 4) included 290 women (543 cycles), respectively.

Among the 256 women included in Group 1, 158 women had unilateral endometrioma and 98 women had bilateral endometriomas (of which 7 had more than two endometriomas). The mean size of endometriomas was 3,669 cm ± 1,518 cm. In the study group, 253 patients were surgically treated for the first time and 3 patients were affected by recurrent endometrioma, therefore they were treated for the second time.

As shown in Table 1, average FSH and LH levels between 2nd and 5th day of the cycle before IVF were significantly higher in women who underwent previous laparoscopic cystectomy for endometrioma (Group 1) compared to unexplained infertility (Group 2), male factor infertility (Group 3) and tubal factor infertility (Group 4); similarly, women who underwent previous laparoscopic cystectomy for endometrioma required

Table 2. Number of retrieved oocytes, developed embryos, fertilisation rate and blastocyst rate per embryos cultured until day 5/6 in women who underwent laparoscopic cystectomy for endometrioma (Group 1), unexplained infertility (Group 2), male factor infertility (Group 3) and tubal factor infertility (Group 4), stratified for age.

	Group 1 (endometrioma)	Group 2 (unexplained infertility)	Group 3 (male factor infertility)	Group 4 (tubal factor infertility)	*p*
No. of oocytes retrieved					
No. of oocytes (*all cycles, n* = 1599)	6.3 ± 3.7 (*n* = 390)	6.9 ± 3.6 (*n* = 294)	7.3 ± 3.7 (*n* = 461)	7.4 ± 3.6 (*n* = 454)	G1 vs G2: .02 G1 vs G3: <.001 G1 vs G4: <.001
<35 years (*cycles, n* = 955)	6.2 ± 3.9 (*n* = 270)	6.8 ± 4.0 (*n* = 161)	7.2 ± 4.2 (*n* = 278)	7.8 ± 3.9 (*n* = 246)	G1 vs G2: .14 G1 vs G3: .005 G1 vs G4: <.0001
35–40 years (*cycles, n* = 554)	6.5 ± 3.2 (*n* = 112)	7.1 ± 3.1 (*n* = 121)	7.4 ± 3.1 (*n* = 144)	7.0 ± 3.3 (*n* = 177)	G1 vs G2: .24 G1 vs G3: .05 G1 vs G4: .36
>40 years (*cycles, n* = 90)	7.4 ± 3.7 (*n* = 8)	6.3 ± 1.7 (*n* = 12)	6.9 ± 2.5 (*n* = 39)	6.3 ± 2.4 (*n* = 31)	G1 vs G2: .27 G1 vs G3: .10 G1 vs G4: .63
No. of embryos developed					
No. of embryos (*all cycles, n* = 1599)	3.6 ± 2.7 (*n* = 390)	3.6 ± 2.5 (*n* = 294)	3.5 ± 2.4 (*n* = 461)	4.1 ± 2.7 (*n* = 454)	G1 vs G2: .97 G1 vs G3: .34 G1 vs G4: .05
<35 years (*cycles, n* = 955)	3.5 ± 2.8 (*n* = 270)	3.7 ± 2.7 (*n* = 161)	3.5 ± 2.6 (*n* = 278)	4.2 ± 2.8 (*n* = 246)	G1 vs G2: .54 G1 vs G3: .62 G1 vs G4: <.005
35–40 years (*cycles, n* = 554)	3.9 ± 2.4 (*n* = 112)	3.6 ± 2.3 (*n* = 121)	3.5 ± 2.3 (*n* = 144)	4.1 ± 2.5 (*n* = 177)	G1 vs G2: .33 G1 vs G3: .18 G1 vs G4: .62
>40 years (*cycles, n* = 90)	2.8 ± 2.4 (*n* = 8)	2.8 ± 1.5 (*n* = 12)	3.6 ± 1.8 (*n* = 39)	4.1 ± 2.5 (*n* = 31)	G1 vs G2: 1 G1 vs G3: .28 G1 vs G4: .23
Fertilisation rate					
Proportion of fertilised oocytes (all cycles)	1467/2469 = 59.4%	1125/2033 = 55.3%	1666/3370 = 49.4%	1944/3348 = 58.1%	G1 vs G2: .006 G1 vs G3: <.0001 G1 vs G4: .30
<35 years	994/1679 = 59.2%	637/1093 = 58.3%	993/2006 = 49.5%	1077/1917 = 56.2%	G1 vs G2: .63 G1 vs G3: <.0001 G1 vs G4: .07
35–40 years	451/731 = 61.7%	451/864 = 52.2%	529/1093 = 48.4%	732/1235 = 59.3%	G1 vs G2: .0001 G1 vs G3: <.0001 G1 vs G4: .29
>40 years	22/59 = 37.3%	37/76 = 48.7%	144/271 = 53.1%	135/196 = 68.9%	G1 vs G2: .04 G1 vs G3: .03 G1 vs G4: <.0001
Blastocyst rate per embryos cultured until day 5/6					
All cycles (*n* = 393)	436/1263 = 34.5%	363/958 = 37.9%	521/1431 = 36.4%	662/1732 = 38.2%	G1 vs G2: .10 G1 vs G3: .31 G1 vs G4: .04
<35 years (*cycles, n* = 273)	296/855 = 34.6%	212/524 = 40.4%	326/852 = 38.2%	403/943 = 42.7%	G1 vs G2: .03 G1 vs G3: .12 G1 vs G4: .0004
35–40 years (*cycles, n* = 112)	134/388 = 34.5%	143/401 = 35.7%	155/453 = 34.2%	228/643 = 35.4%	G1 vs G2: .74 G1 vs G3: .92 G1 vs G4: .76
>40 years (*cycles, n* = 8)	6/20 = 30.0%	8/33 = 24.2%	40/126 = 31.7%	31/116 = 26.7%	G1 vs G2: .65 G1 vs G3: .89 G1 vs G4: .76

Data are expressed as means ± standard deviations for continuous variables, and as percentages for dichotomous variables.

significantly higher doses of gonadotrophins during ovarian stimulation compared to other types of infertility, although this effect was non-significant considering age over 40 years.

As reported in Table 2, the number of oocytes retrieved during the pick-up was significantly lower in women who underwent previous laparoscopic cystectomy for endometrioma compared to male factor and tubal factor infertility, although also this difference seems to be attenuated considering age over 40 years. Conversely, the number of embryos developed does not show significant differences between women with previous endometriomas and other types of infertility, besides a small significance only before 35 years of age compared to tubal factor infertility. The fertilisation rate, considering all the cycles, was significantly higher in women who underwent previous laparoscopic cystectomy for endometrioma compared to unexplained infertility and male factor infertility. In addition, the blastocyst rate per embryo cultured until day 5/6 did show significant differences, when considering all the cycles.

Finally, we did not find significant differences between the endometrioma group and the other types of infertility regarding embryo utilisation (defined as the proportion of all transferred and cryopreserved embryos per number of all obtained embryos, regardless of the day of transfer or of

Table 3. Embryo utilisation, pregnancy and delivery rates in women who underwent laparoscopic cystectomy for endometrioma (Group 1), unexplained infertility (Group 2), male factor infertility (Group 3) and tubal factor infertility (Group 4), stratified for age.

	Group 1 (endometrioma)	Group 2 (unexplained infertility)	**Group 3 (male factor infertility)**	**Group 4 (tubal factor infertility)**	*p*
Embryo utilisation rate					
All cycles (*n* = 393)	747/1412 = 52.9%	563/1062 = 53.0%	891/1609 = 55.4%	977/1879 = 52.0%	G1 vs G2: 1 G1 vs G3: .17 G1 vs G4: .60
<35 years (*n* = 273)	511/954 = 53.6%	315/594 = 53.0%	533/958 = 55.6%	547/1033 = 53.0%	G1 vs G2: .84 G1 vs G3: .36 G1 vs G4: .79
35–40 years (*cycles*, *n* = 112)	226/436 = 51.8%	231/435 = 53.1%	275/512 = 53.7%	368/719 = 51.2%	G1 vs G2: .71 G1 vs G3: .57 G1 vs G4: .82
>40 years (*cycles*, *n* = 8)	10/22 = 45.5%	17/33 = 51.5%	73/139 = 52.5%	62/127 = 48.8%	G1 vs G2: .66 G1 vs G3: .54 G1 vs G4: .78
All cycles (*n* = 393)	747/1412 = 52.9%	563/1062 = 53.0%	891/1609 = 55.4%	977/1879 = 52.0%	G1 vs G2: 1 G1 vs G3: .17 G1 vs G4: .60
Pregnancy rate					
% pregnancies/ ET (*ET*, *n* = 1409)	30.7 (*n* = 339)	30.7 (*n* = 254)	31 (*n* = 406)	32.7 (*n* = 410)	G1 vs G2: 1 G1 vs G3: .92 G1 vs G4: .56
<35 years (*ET*, *n* = 827)	30.3 (*n* = 232)	33.6 (*n* = 137)	31.8 (*n* = 242)	33.3 (*n* = 216)	G1 vs G2: .51 G1 vs G3: .71 G1 vs G4: .49
35–40 years (*ET*, *n* = 503)	35.2 (*n* = 102)	28 (*n* = 107)	31.8 (*n* = 129)	32.7 (*n* = 165)	G1 vs G2: .28 G1 vs G3: .60 G1 vs G4: .69
>40 years (*ET*, *n* = 79)	60 (*n* = 5)	20 (*n* = 10)	22.9 (*n* = 35)	27.6 (*n* = 29)	G1 vs G2: .25 G1 vs G3: .12 G1 vs G4: .30
Delivery rate					
% deliveries/ ET (*ET*, *n* = 1409)	18 (*n* = 339)	18.9 (*n* = 254)	20.4 (*n* = 406)	22.7 (*n* = 410)	G1 vs G2: .78 G1 vs G3: .40 G1 vs G4: .11
<35 years (*ET*, *n* = 827)	16 (*n* = 232)	21.9 (*n* = 137)	18.6 (*n* = 242)	24.5 (*n* = 216)	G1 vs G2: .61 G1 vs G3: .46 G1 vs G4: .02
35–40 years (*ET*, *n* = 503)	25 (*n* = 102)	16.8 (*n* = 107)	24.8 (*n* = 129)	20 (*n* = 165)	G1 vs G2: .16 G1 vs G3: 1 G1 vs G4: .35
>40 years (*ET*, *n* = 79)	40 (*n* = 5)	0 (*n* = 10)	17.1 (*n* = 35)	24.1 (*n* = 29)	G1 vs G2: .095 G1 vs G3: .56 G1 vs G4: .59

Data are expressed as percentages; ET: embryo transfer.

cryopreservation), pregnancy and delivery rates, regardless of age (Table 3).

Discussion

The main focuses of endometriosis surgical treatment are to ameliorate of woman's symptoms (Laganà et al. 2016; Raffaelli et al. 2018), the prevention of disease progression and the improvement of fertility rates. In our setting, about 60% of treated women will conceive spontaneously after surgical treatment of endometriosis-associated infertility (Ban Frangez et al. 2017; Šalamun et al. 2018); when there is no spontaneous conception after 6–12 months after the surgical treatment, women are usually addressed to IVF techniques. Nevertheless, IVF could be considered immediately after the surgical treatment when the ovarian reserve is low or in the case of concurrent tubal or male factor infertility.

The presence of ovarian endometrioma is usually associated with moderate or severe disease, according to the revised American Society for Reproductive medicine (rASRM) classification (Chapron et al. 2009; Barra et al. 2020); indeed, ovarian endometrioma can be found in up to 17–44% women with endometriosis (Noventa et al. 2019; Kwok et al. 2020).

The pathogenesis of ovarian endometriomas remains to be elucidated, but they are mostly thought to occur through implantation and subsequent invagination of endometriotic cells through the ovarian serosa, during the remodelling of the ovarian cortex after ovulation (Young et al. 2013). The exact reason why the presence of endometrioma, often linked to peritoneal disease, decreases the fertility potential remains still debated. On the one hand, endometrioma can play a direct detrimental role distorting the tubo-ovarian anatomy; on the other hand, the enhanced release of pro-inflammatory cytokines and oxidative stress may impair ovarian function, resulting in defective folliculogenesis, reduced quality of the oocytes with impaired fertilisation capacity, and finally reduced embryo quality with low implantation potential (Agarwal et al. 2012; Filipchiuk et al. 2020; Laganà et al. 2020).

The impact of endometriomas on ovarian stimulation in IVF procedures remains unclear (Terzic et al. 2020). Minimally invasive surgical excision of endometriomas with stripping technique prior to IVF procedure is widely practiced, even though very little evidence exists to provide a strong guideline to clinicians. Surgical treatment could restore distorted tubo-ovarian anatomy and therefore eases the retrieval of the oocytes; nevertheless, recently concerns have been raised about the possibility to reduce ovarian reserve during excision of the endometrioma, with a potentially detrimental effect on IVF reproductive outcomes. The pathogenetic mechanism mediating the injury to the ovarian reserve may be due to several factors: first, the stripping procedure may determine the accidental damage of healthy ovarian tissue and primordial follicles adjacent to the cyst wall (Raffi et al. 2012); addition, thermal damage may occur during coagulation of small bleeding vessels within the ovarian parenchyma (Somigliana et al. 2012; Muzii et al. 2014).

On the other side, conservative management is not without potential drawbacks and risks as well. As already highlighted by Somigliana et al. (Somigliana et al. 2015), the presence of the endometrioma is thought to increase difficulties during oocyte retrieval, may reduce the quality of the oocytes and may interfere with ovarian responsiveness to ovarian hyperstimulation. Furthermore, ovarian endometriomas may become infected in case of an accidental puncture during oocyte retrieval, and this element may play a negative role in reproductive outcomes. In addition, avoiding surgery increases the risk of missing occult malignancies or causing cancer development later in life (Králíčková et al. 2020).

In a prospective study (Coccia et al. 2014), Coccia and colleagues investigated the relationships between ovarian endometrioma size, ovarian responsiveness and the number of retrieved oocytes following ovarian stimulation. In this study, an endometrioma size of 3 cm has been found able to influence the ovarian response to stimulation. Similarly, other authors (Esinler et al. 2012) suggested that endometriomas of 3 cm or less in diameter did not have a deleterious effect on ovarian reserve in Intracytoplasmic Sperm Injection (ICSI) cycles.

Nevertheless, women with endometrioma undergoing IVF/ICSI compared with women without endometrioma has similar clinical pregnancy rates and similar live birth rates, but a lower mean number of oocytes retrieved and a higher cancellation rate; in addition, women with endometrioma requires usually higher dosage for stimulation and have lower antral follicle count, suggesting that their ovarian reserve can be diminished even before IVF/ICSI (Hamdan et al. 2015; Nickkho-Amiry et al. 2018). In addition, recent data suggest that recurrent endometriomas do not have a worse impact on ART outcome than primary endometriomas, and repeated surgery has a higher risk for complications (Ata et al. 2017), so conservative management without surgery can be justified in case of recurrent endometriomas.

Our study was designed to elucidate the impact of surgical treatment of endometrioma on reproductive outcomes in women undergoing IVF, compared with women with unexplained infertility, tubal factor or male factor infertility. In the setting where the study was performed, all infertile women undergo laparoscopy, and endometriosis is systematically excised when found: according to this protocol, about 50% of women with endometriosis-associated infertility are able to achieve spontaneous pregnancy within 6–12 months; when pregnancy does not occur within this timeframe, or when the ovarian reserve is already low, women are addressed to IVF. In this context, we found that women who underwent previous laparoscopic cystectomy for endometrioma have higher FSH and LH levels between the 2nd and 5th day of the cycle before IVF, need higher doses of gonadotrophins for ovarian stimulation and have a lower number of retrieved oocytes compared with other types of infertility. Nevertheless, these negative effects of endometriosis do not reflect on pregnancy and delivery rates, which remain fully comparable and overlapping with other causes of infertility. In addition, differences for ovarian stimulation parameters and reproductive outcomes after IVF between endometriosis and other types of infertility lost significance with the increase of women's age: indeed, in the case of women older than 35 years, the higher need for gonadotrophins, as well as the lower number of retrieved oocytes, is a common background, regardless of endometriosis.

To the best of our knowledge, this is the first study in which all women underwent laparoscopy before the first IVF attempt, in order to restore the anatomical conditions and allow spontaneous pregnancy. Nevertheless, we acknowledge that we did not evaluate the AMH levels before and after surgery, and this may be considered a limitation of the study, together with the retrospective design. In addition, we did not compare FSH levels before and after surgery. On that basis, we solicit future investigations in order to confirm our findings in a large cohort analysis.

Ethical approval

The study was approved by the National Medical Ethics Committee of Slovenia (Approval ID: 0120-174/2018/6).

Author contributions

All the authors conform to the Journal and the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, contributed to the intellectual content of the study and gave approval for the final version of the article.

Disclosure statement

The authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company. The authors alone are responsible for the content and writing of the paper.

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References

Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. 2012. The effects of oxidative stress on female reproduction: a review. Reproductive Biology and Endocrinology 10:49.

Ata B, Mumusoglu S, Aslan K, Seyhan A, Kasapoglu I, Avci B, et al. 2017. Which is worse? Comparison of ART outcome between women with primary or recurrent endometriomas. Human Reproduction 32: 1427–1431.

Ban Frangez H, Korošec S, Pozlep B, Jancar N, Salamun V, Vogler A, et al. 2017. Spontaneous pregnancy rates after reproductive surgery. Reproductive Biomedicine Online 35:165–173.

Barra F, Biscaldi E, Scala C, Laganà AS, Vellone VG, Stabilini C, et al. 2020. A prospective study comparing three-dimensional rectal water contrast transvaginal ultrasonography and computed tomographic colonography in the diagnosis of rectosigmoid endometriosis. Diagnostics 10:252.

Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I. et al. 2015. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Medicine 12:e1001885.

Chapron C, Pietin-Vialle C, Borghese B, Davy C, Foulot H, Chopin N. 2009. Associated ovarian endometrioma is a marker for greater severity of deeply infiltrating endometriosis. Fertility and Sterility 92:453–457.

Coccia ME, Rizzello F, Barone S, Pinelli S, Rapalini E, Parri C, et al. 2014. Is there a critical endometrioma size associated with reduced ovarian responsiveness in assisted reproduction techniques? Reproductive BioMedicine Online 29:259–266.

Dunselman GAJ, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B. et al. 2014. ESHRE guideline: management of women with endometriosis. Human Reproduction 29:400–412.

Esinler I, Bozdag G, Arikan I, Demir B, Yarali H. 2012. Endometrioma ≤3 cm in diameter per se does not affect ovarian reserve in intracytoplasmic sperm injection cycles. Gynecologic and Obstetric Investigation 74:261–264.

Filipchiuk C, Laganà AS, Beteli R, Ponce TG, Christofolini DM, Martins Trevisan C, et al. 2020. BIRC5/survivin expression as a non-invasive biomarker of endometriosis. Diagnostics 10:533.

Gardner DK, Lane M, Stevens J, Schlenker T, Schoolcraft WB. 2000. Blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer. Fertility and Sterility 73:1155–1158.

Giudice LC. 2010. Clinical practice. Endometriosis. The New England Journal of Medicine 362:2389–2398.

Greene AD, Lang SA, Kendziorski JA, Sroga-Rios JM, Herzog TJ, Burns KA. 2016. Endometriosis: where are we and where are we going? Reproduction 152:R63–R78.

Hamdan M, Dunselman G, Li TC, Cheong Y. 2015. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. Human Reproduction Update 21:809–825.

Hirsch M, Begum MR, Paniz É, Barker C, Davis CJ, Duffy J. 2018. Diagnosis and management of endometriosis: a systematic review of international and national guidelines. BJOG: An International Journal of Obstetrics and Gynaecology 125:556–564.

Kasapoglu I, Ata B, Uyaniklar O, Seyhan A, Orhan A, Yildiz Oguz S, Uncu G. 2018. Endometrioma-related reduction in ovarian reserve (ERROR): a prospective longitudinal study. Fertility and Sterility 110:122–127.

Korosec S, Ban Frangez H, Verdenik I, Kladnik U, Kotar V, Virant-Klun I, Vrtacnik Bokal E. 2014. Singleton pregnancy outcomes after in vitro fertilization with fresh or frozen-thawed embryo transfer and incidence of placenta praevia. BioMed Research International 2014: 431797.

Králíčková M, Laganà AS, Ghezzi F, Vetvicka V. 2020. Endometriosis and risk of ovarian cancer: what do we know? Archives of Gynecology and Obstetrics 301:1–10.

Kwok H, Jiang H, Li T, Yang H, Fei H, Cheng L, et al. 2020. Lesion distribution characteristics of deep infiltrating endometriosis with ovarian endometrioma: an observational clinical study. BMC Women's Health 20:111.

Laganà AS, Garzon S, Götte M, Viganò P, Franchi M, Ghezzi F, Martin DC. 1975. The pathogenesis of endometriosis: molecular and cell biology insights. International Journal of Molecular Sciences 20(22):5615.

Laganà AS, La Rosa VL. 2020. Multidisciplinary management of endometriosis: current strategies and future challenges. Minerva Medica 111: 18–20.

Laganà AS, Salmeri FM, Ban Frangež H, Ghezzi F, Vrtačnik-Bokal E, Granese R. 2020. Evaluation of M1 and M2 macrophages in ovarian endometriomas from women affected by endometriosis at different stages of the disease. Gynecological Endocrinology 36:441–444.

Laganà AS, Vitale SG, Trovato MA, Palmara VI, Rapisarda AMC, Granese R, et al. 2016. Full-thickness excision versus shaving by laparoscopy for intestinal deep infiltrating endometriosis: rationale and potential treatment options. BioMed Research International 2016:3617179.

Lessey BA, Gordts S, Donnez O, Somigliana E, Chapron C, Garcia-Velasco JA, Donnez J. 2018. Ovarian endometriosis and infertility: in vitro fertilization (IVF) or surgery as the first approach? Fertility and Sterility 110: 1218–1226.

Muzii L, Di Tucci C, Di Feliciantonio M, Marchetti C, Perniola G, Panici PB. 2014. The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: a systematic review and meta-analysis. Human Reproduction 29:2190–2198.

Nickkho-Amiry M, Savant R, Majumder K, Edi-O'sagie E, Akhtar M. 2018. The effect of surgical management of endometrioma on the IVF/ICSI outcomes when compared with no treatment? A systematic review and meta-analysis. Archives of Gynecology and Obstetrics 297: 1043–1057.

Noventa M, Scioscia M, Schincariol M, Cavallin F, Pontrelli G, Virgilio B, et al. 2019. Imaging modalities for diagnosis of deep pelvic endometriosis: comparison between trans-vaginal sonography, rectal endoscopy sonography and magnetic resonance imaging. a head-to-head meta-analysis. Diagnostics 9(4):225.

Parazzini F, Esposito G, Tozzi L, Noli S, Bianchi S. 2017. Epidemiology of endometriosis and its comorbidities. European Journal of Obstetrics, Gynecology, and Reproductive Biology 209:3–7.

Raffaelli R, Garzon S, Baggio S, Genna M, Pomini P, Laganà AS, et al. 2018. Mesenteric vascular and nerve sparing surgery in laparoscopic segmental intestinal resection for deep infiltrating endometriosis. European Journal of Obstetrics, Gynecology, and Reproductive Biology 231:214–219.

Raffi F, Metwally M, Amer S. 2012. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. The Journal of Clinical Endocrinology and Metabolism 97: 3146–3154.

Šalamun V, Verdenik I, Laganà AS, Vrtačnik-Bokal E. 2018. Should we consider integrated approach for endometriosis-associated infertility as gold standard management? Rationale and results from a large cohort analysis. Archives of Gynecology and Obstetrics 297:613–621.

Shafrir AL, Farland LV, Shah DK, Harris HR, Kvaskoff M, Zondervan K, Missmer SA. 2018. Risk for and consequences of endometriosis: a critical epidemiologic review. Best Practice & Research. Clinical Obstetrics & Gynaecology 51:1–15.

Somigliana E, Benaglia L, Paffoni A, Busnelli A, Vigano P, Vercellini P. 2015. Risks of conservative management in women with ovarian endometriomas undergoing IVF. Human Reproduction Update 21: 486–499.

Somigliana E, Berlanda N, Benaglia L, Viganò P, Vercellini P, Fedele L. 2012. Surgical excision of endometriomas and ovarian reserve: a systematic review on serum antimüllerian hormone level modifications. Fertility and Sterility 98:1531–1538.

Terzic M, Aimagambetova G, Garzon S, Bapayeva G, Ukybassova T, Terzic S, et al. 2020. Ovulation induction in infertile women with endometriotic ovarian cysts: current evidence and potential pitfalls. Minerva Medica 111:50–61.

Viganò P, Parazzini F, Somigliana E, Vercellini P. 2004. Endometriosis: epidemiology and aetiological factors. Best Practice & Research. Clinical Obstetrics & Gynaecology 18:177–200.

Young VJ, Brown JK, Saunders PTK, Horne AW. 2013. The role of the peritoneum in the pathogenesis of endometriosis. Human Reproduction Update 19:558–569.