

# The Impact of Ovarian Endometrioma(s) on ART Outcomes: Retrospective Case Control Study

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## ABSTRACT

**OBJECTIVE:** To compare oocyte yield of women with intact ovarian endometrioma(s) to those without endometrioma undergoing ART. Secondary outcomes were implantation and live birth rates between the two groups.

**STUDY DESIGN:** Retrospective case-control study was conducted to document eligible cases. A total of 165 women with intact endometrioma(s) (END) were included in the final analysis. Total of 196 cases with tubal factor infertility who underwent ART in the same time period were included as controls (CONT group). Cases and controls were matched for age, BMI and serum AMH concentrations. Ovarian stimulation characteristics and pregnancy outcomes including live birth data were documented for both groups.

**RESULTS:** Despite similar demographic characteristics, significantly longer cycle duration and higher amounts of gonadotropin consumption was observed in END group compared to controls ( $p < 0.001$ ). Significantly lower number of retrieved oocytes, mature oocytes and mature oocyte fraction (%), no of retrieved/mature) were detected in END group. There was no statistically significant difference in terms of fertilization, implantation and live birth rate per started cycle among groups. Cycle cancellations were also similar.

**CONCLUSION:** In women with intact ovarian endometrioma(s) undergoing ART, oocyte quantity, especially mature oocyte yield was hampered. However, adequate number of mature oocytes, successful fertilization and satisfactory implantation rates might be possible contributing to acceptable live births. Further randomized controlled trials of patients with different sizes of endometrioma(s) would be needed to confirm our conclusions.

**Keywords:** Assisted reproductive technologies, Endometrioma, Fertilization, Intracytoplasmic sperm injection, Implantation

*Gynecol Obstet Reprod Med 2016;22(2):84-89 DOI: 10.21613/GORM.2016.63*

## Introduction

Endometriosis is a serious health burden affecting 0.8-2% of women at a reproductive age (1). The disease is closely associated with infertility as up to half of infertile women get diagnosed with endometriosis (2,3). A staging system (American Society of Reproductive Medicine Endometriosis Classification) is currently being used to document the severity of the condition and to counsel patients as well (4). Accumulating evidence suggests that advanced stage disease

(III-IV) is associated with poorer reproductive outcomes when compared to earlier stages in women undergoing assisted reproductive technologies (ART) (5,6). Advanced stage endometriosis may exist in several forms and is rather a heterogeneous group. Ovarian endometrioma is another clinical entity that is present in 20-40% of women with endometriosis (7). Some authors have demonstrated poor ART outcomes in the presence of endometrioma(s) (8); however others have failed to show any detrimental effect on outcomes (9). In this view, infertile women with documented ovarian endometrioma(s) require special attention.

Endometrioma(s) can be identified by transvaginal sonography with high sensitivity and specificity without emerging diagnostic laparoscopy (10,11). Resection of endometrioma(s) prior to ART is controversial. European Society of Human Reproduction and Embryology (ESHRE) guidelines for the diagnosis and treatment of endometriosis recommends laparoscopic surgery before IVF/ICSI in the treatment of symptomatic women with endometrioma and in asymptomatic patients with endometriomas  $\geq 4$  cm (12). In the context of dis-

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Submitted for Publication: 19.03.2016

Accepted for Publication: 20.04.2016

cussing beneficial effect of surgery, a meta-analysis revealed no significant difference in pregnancy rates or in gonadotropin responses between the surgical management and control groups prior to in-vitro fertilization (IVF) (13). In a more recent Cochrane review, lack of any benefit from either aspiration or cystectomy with regard to clinical pregnancy rates or the number of mature oocytes retrieved was reported when compared to expectant management (14). Besides, accumulating evidence suggests that surgery has a detrimental impact on ovarian reserve in terms of serum Anti-Mullerian hormone (AMH) levels and overall response to ovarian stimulation (OS) (15-17). Accordingly, increasing numbers of authors advocate against surgery prior to ART unless there is refractory pain, significant malignancy potential or inaccessibility to follicles during oocyte retrieval.

As a matter of fact, more and more infertile women with intact ovarian endometrioma(s) are likely to enter an ART programme without having surgery. Hence, there is a need for studies evaluating the noticeable impact of intact ovarian endometrioma(s) on ART outcomes, especially on oocyte yield during ovarian stimulation.

## Material and Method

A chart review of an ART center was performed to detect eligible cases between January 2009 and August 2014. Complete data is comprised of the first intracytoplasmic sperm injection (ICSI) cycle of each couple. All included patients met the following inclusion criteria: subjects between the age of 18 and 40, requiring ART with an indication of primary infertility (women with intact ovarian endometrioma in either ovaries or requiring ART due to tubal factor infertility), women's body mass index (BMI) between 18 and 34 kg/m<sup>2</sup>, thyroid stimulating hormone (TSH) levels <4,5 IU/ml. Exclusion criteria were: 1) subjects with diminished ovarian reserve, according to the Bologna criteria (18); 2) subjects with documented Mullerian and/or uterine anomaly; 3) GnRH-agonist down regulation longer than 1 month or oral contraceptive use prior to OS; 4) severe oligozoospermia or azoospermia cases; 5) Pre-implantation genetic screening and frozen-thaw embryo transfer cycles; 6) other ovarian cystic appearance rather than endometrioma during transvaginal sonography; 7) women with endometrioma larger than 6 cm prior to ART. Primary outcome of the study is to compare oocyte yield of women with intact ovarian endometrioma(s) to those without endometrioma undergoing ART. Secondary outcomes were implantation and live birth rates.

During the period, 165 women were detected to have intact ovarian endometrioma(s) while undergoing their first OS cycle without prior surgery (END group). Endometrioma(s) were encountered in the baseline scan for all cases. Ultrasound diagnosis of ovarian endometrioma was based on the visualization of round-shaped homogeneous hypo echoic appearance

of low-level echoes within the ovary as previously described (19). The endometrioma was measured in three dimensions, and the average diameter was calculated. Total of 196 cases with tubal factor infertility who underwent ART in the same time period were included as controls (CONT group). Bilateral abnormal tubal patency was documented in all women with hysterosalpingography (HSG) within 3 months of OS. Controls were matched with cases for age, BMI and serum AMH concentrations.

### Ovarian Stimulation Protocol

The study is comprised of one stimulation cycle of each subject in order to prevent possible crossover bias and assignment of subjects to any OS protocol is made by physicians' discretion. Ovarian stimulation was carried out either with GnRH-antagonist (Cetrotide, Merck Serono) (0.25 mg/day) which was initiated when the leading follicle size >12mm during follicular phase or with GnRH-agonist which was administered on the 21st day of the preceding cycle and then reduced by half when down-regulation was achieved (serum estradiol level <50 pg/mL). Gonadotropin was initiated (hMG (Menogon, Ferring) or recombinant FSH (Gonal-F, Merck Serono)) beginning from the second day of the menstrual cycle with a starting dose of 150-300 IU/day according to the patient's ovarian reserve and body mass index. When at least three follicles were  $\geq$  18mm, rhCG (250  $\mu$ g; Ovitrelle, Merck Serono) was used for final oocyte maturation. Transvaginal ultrasound-guided oocyte retrieval and embryo transfer procedure was performed as described elsewhere (20). Manipulations targeting the endometrioma(s) were avoided during the retrieval procedure. One or 2 embryos were transferred. Top quality embryos were defined as those with  $\geq$ 7 evenly sized cells and  $\leq$ 10% fragmentation on day 3 and with  $\geq$ 3 AA quality of blastocyst morphology on day 5. During the study period, 1 embryo was transferred to patients aged <35 years; in patients aged  $\geq$ 35 years, 2 embryos were transferred, in accordance with local legislation. Clinical pregnancy was defined as the presence of a gestational sac with an embryonic pole and positive heart beat at 7 weeks of gestation and ongoing pregnancy was defined as the presence of an intrauterine sac with an embryonic pole demonstrating cardiac activity at 10 weeks of gestation.

### Statistical Analysis

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by Kolmogorov Smirnov test. Data were shown as mean  $\pm$  SD or number of cases and (%). Mean differences between groups were compared by Student's t test whereas Mann Whitney U test was applied for the comparison of median values. Nominal data was analyzed by Pearson's chi-square or Fisher's exact test, where applicable. Correlation analysis was conducted using a Spearman's rank test. A p value less than 0.05 was considered statistically significant.

## Results

Both groups were compared in terms of OS outcomes, oocyte yield (number of retrieved and mature oocytes), clinical pregnancy rates, live birth rates, cancellations and miscarriages. Cycle cancellations were performed due to lack of ovarian response, fertilization failure or in the presence of no available embryos for transfer.

According to demographic characteristics, mean age, infertility duration, serum AMH levels, basal antral follicle count and TSH levels were similar among groups. Approximately 81% of subjects in END group had unilateral, whereas 19% had bilateral endometriomas. The median diameter of ovarian endometrioma was 3 (1-6) cm. Total progressive motile sperm count (sperm concentration/ml X volume (ml) X motility (+4 fraction)) of the groups was statistically similar ( $p>0,05$ ). In END group, 79% (130/165) of subjects underwent OS with agonist and 21% (35/165) of them underwent with antagonist protocol. Demographic characteristics of groups are shown in Table 1.

Significantly higher amount of gonadotropin ( $2978\pm1135$

vs.  $2022\pm749$  IU) and higher cycle duration (11,2 vs. 9,9 days) was detected in END group ( $p<0,001$ ). Significantly lower number of retrieved oocytes ( $6.5\pm2.6$  vs.  $9.0\pm5.7$ ), mature oocytes ( $3.5\pm2.5$  vs.  $6.7\pm4.2$ ) and mature oocyte fraction % (no of retrieved/mature) (53.7% vs. 78.5%) were detected in END group, when compared to controls ( $p<0,001$ ). There was no statistical difference in terms of implantation, ongoing pregnancy rate/started cycle (OPR) and live birth rate/started cycle (LBR) among groups. Cycle cancellations were also similar between groups. Cycle characteristics and pregnancy outcomes of groups are shown in Table 2 and in Table 3. In END group, OPR (22,3% with antagonist, 14,3% with agonist;  $p=0,298$ ) and LBR (21,5% with antagonist, 14,3% with agonist;  $p=0,341$ ) were similar in both OS protocols.

According to endometrioma localization, there were similar mature oocytes obtained either in subjects with bilateral or with unilateral endometriomas ( $2.9\pm2.7$  vs.  $3.6\pm2.5$  respectively,  $p=0,176$ ). Relatively higher OPR (6,4% vs. 19,4%,  $p=0,083$ ) and LBRs (6,4% vs. 17,9%,  $p=0,170$ ) were detected in subjects with unilateral disease, however the difference did not reach statistical significance.

Table 1: Demographic characteristics of the groups

	END Group (n:165)	Control Group (n:196)	p value
Age (years)	34.33±5.36	33.24±5.25	0.068
Duration of marriage (years)	5 (1-16)	7 (1-14)	0.053
AMH (ng/mL)	2.50 (1-7)	3 (1-5)	0.081
AFC (n)	9.32±3.37	9.64±3.02	0.354
TSH (mU/L)	1.80 (0.45-4.5)	1.82 (0.25-4.5)	0.423
TPMSC (x106)	50 (9-234)	45 (10-230)	0.572
Unilateral endometrioma, n (%)	134/165 (81.3)	-	
Bilateral endometrioma, n (%)	31/165 (18.7)	-	
Endometrioma size (cm)	3 (1-6) 3.2±1.2	-	

Values are expressed as mean ± standard deviation, \*Values are expressed as median with minimum value and maximum value parenthesis. Statistically significant p-values are in bold.

AMH: Anti mullerian hormone, AFC: Antral follicle count, TSH: Thyroid stimulating hormone, TPMSC: Total progressive motile sperm count

Table 2: Ovarian stimulation outcomes of the groups

	END Group (n:165)	Control Group (n:196)	p value
Total dose (IU)	2.978.58±1135.69	2.022.90±749.23	<b>&lt;0.001</b>
E2 on hCG day (pg/mL)	1.690 (5-5625)	1.905.50 (72-5670)	0.051
Endometrial thickness (mm)	10.25±1.93	10.70±2.19	0.054
Total duration (days)	11.24±2.12	9.99±2.93	<b>&lt;0.001</b>
Number of retrieved oocytes (n)	6.54±2.64	9.06±5.75	<b>&lt;0.001</b>
Mature (MII) (n)	3.50±2.59	6.76±4.28	<b>&lt;0.001</b>
MI %	53.7±29.55	78.54±24.85	<b>&lt;0.001</b>
Fertilization %	61.86±33.78	68.06±29.65	0.067

Values are expressed as mean ± standard deviation, \*Values are expressed as median with minimum value and maximum value parenthesis. Statistically significant p-values are in bold.

E2: Estradiol, MII: Mature

Table 3: Ovarian stimulation and pregnancy outcomes of the groups

	END Group (n:165)	Control Group (n:196)	p value
Implantation rate	16.61±33.77	20.75±35.05	0.255
Clinical pregnancy rate, n (%)	35 (21.2)	59 (30.1)	0.055
Ongoing pregnancy rate, n (%)	34 (20.6)	56 (28.6)	0.081
Live Birth, n (%)	33 (20.0)	51 (26.0)	0.177
Miscarriages, n (%)	2 (1.2)	9 (4.6)	0.063
Cycle cancellation, n (%)	17 (10.3)	16 (8.2)	0.482

Values are expressed as mean ± standard deviation

According to Spearman's analysis, negative correlation was detected between endometrioma size and oocyte yield both in terms of total number of retrieved ( $r = -0.129$ ,  $p=0.103$ ) and mature oocytes ( $p= -0.116$ ,  $p=0.142$ ), where differences are not statistically significant.

During OS, there were 4 mild pelvic inflammatory diseases encountered which was associated with the oocyte retrieval procedure. All cases were managed in the outpatient clinic with oral antibiotics without any complication. There were no septic conditions detected including pelvic abscess requiring hospitalization during the study period.

## Discussion

Based on the findings of the current study, women with intact endometrioma(s) are likely to reveal lower number of oocytes during OS resulting with decreased number of mature oocytes. This relatively low ovarian response is observed even with higher gonadotropin consumption and longer duration. However, if obtained, fertilization and implantation rates were not compromised when compared to controls. Accordingly, live birth rates were not hampered despite lower oocyte yield in the presence of endometrioma(s).

To date, few studies have specifically examined the ART outcomes of women with intact endometrioma(s) regardless of stage. In those studies, endometrioma cases were compared to that of other infertility etiologies including male or tubal factor infertility (8,21-23). A recent two meta-analysis have focused on the OS characteristics and ART outcomes of women with intact endometriomas (6,24). According to Hamdan et al, women with intact endometrioma revealed lower number of retrieved oocytes when compared to women with no endometriosis (SMD -0.23; 95% CI (-0.37, -0.10) (6). Similarly, pooled data from the meta-analysis of Yang et al revealed 1.50 fewer oocytes retrieved in women with ovarian endometrioma than in those without endometrioma (WMD -1.50; 95% CI -2.84 to -0.15,  $P=0.03$ ) (24). Authors also provided information about embryos, as they suggested a reduction in good-quality forms in patients with endometrioma. In our study, significantly lower oocytes were harvested in women with endometrioma despite higher gonadotropin usage

and longer duration. Mature oocyte fraction was also found to decrease in END group. Interestingly, in our study and in the meta-analyses, implantation and live birth rates were found to be similar among those with or without endometriomas. Such results allow speculation that the ovarian endometriosis per se exerts some detrimental impact on the oocyte quantity rather than quality. In our data, mature oocyte number was lower in END group, but fertilization and implantation rates were similar. This might be suggestive of a theory as existence of endometrioma may compromise the oocyte quantity rather than fertilization or implantation capacity. If we could obtain adequate number of oocytes from the ovary with endometrioma, successful implantation can be achieved. Supportively, it has recently been shown that the presence of endometrioma does not compromise time-lapse morphokinetics of embryos (25). Decreased oocyte quantity might be due to some molecular detrimental interactions caused by cytokines, mechanical distortion of ovarian cortex or by oxidative stress contributing to relatively decreased ovarian response, mainly induced by the presence of endometrioma discussed previously (24). These mechanisms may contribute to decreased ovarian response, but in the availability of enough mature oocyte, fertilization and implantation capacity seems not to be compromised, resulting with live births. Similar fertilization, implantation and live birth rates either in our study or in the above mentioned meta-analyses further indicate that the oocyte quality seems not to be hampered by the endometrioma.

In women undergoing ART, the optimal management of endometriomas is still debated. According to the ESHRE guidelines, laparoscopic surgery before IVF/ICSI is considered to be the 'gold standard' in the treatment of symptomatic endometriomas (12). On the other hand, surgery indeed has a detrimental impact on ovarian reserve in terms of serum AMH levels and overall response to OS (15-17), despite enough surgical experience (26-28). In this context, size of the endometrioma seems to be the crucial determinant in management. Esinler et al. demonstrated that the unilateral endometriomas  $\leq 3$  cm in diameter did not have a deleterious effect on ovarian reserve in ICSI cycles (29). Recently, Cocia et al. observed a critical endometrioma size of 3 cm, in those with unilateral cyst, above this size, which the total numbers of follicles and retrieved oocytes were negatively affected

(26). For every millimeter of increase in endometrioma size, the predicted number of retrieved oocytes was shown to decrease by 0,667. We documented significantly lower oocyte yield with the mean endometrioma diameter of 3.2 cm ( $\pm 1.2$  SD) that is consisted with of findings of Cocia et al. Those in END group had mature oocytes which were one half as low as those of a control group. Negative correlation was also documented between endometrioma size and oocyte yield, in terms of total number of retrieved and mature oocytes, however this difference was not statistically significant all of the above studies have evaluated unilateral cases and compared the overall response with that of contralateral ovaries. In our study, not all but 81% of endometriomas were unilateral. Nevertheless, we did not evaluate the response of contralateral ovary in each subject, as this is the limitation of the current study. Size limit of 3 cm, particularly in those with a unilateral cyst should be taken into account even deciding for conservative management or surgery. This finding seems to be more important especially in those with reduced ovarian reserve.

Obviously, there is a need for studies evaluating the efficacy of different OS protocols particularly for this special population. Administration of GnRH agonists for a period of three to six months prior to ART has been shown to increase pregnancy odds (30). However, this analysis was limited only to 3 studies without specifically examining those with intact endometrioma(s). There is currently no solid evidence to support a routine use of a particular OS protocol, despite few studies that have revealed similar pregnancy outcomes either with agonists or antagonists (31,32). In our study, both OS protocols yielded comparable OPR and LBRs in END group without any significant difference. However, randomized and adequately powered studies are necessary to drive a conclusion.

Moreover, in the case of a conservative approach, the risk of an ovarian abscess after ovarian puncture during ultrasound-guided oocyte retrieval should be taken into account. According to Somigliana et al. (33), several drawbacks including septic complications, technical difficulties or occult malignancy risk might be associated with the conservative approach. Late pregnancy complications following aspiration of endometrioma have also been reported in the literature (34). In our study, we did not observe severe complications except few mild pelvic infections, however long term careful follow-up is necessary for women, particularly when consecutive ART cycles are decided. On the potential benefits and harms of both conservative management and surgery to share the consequences of decision.

In conclusion, oocyte quantity was hampered during OS when there is ovarian endometrioma(s). However, if OS results with adequate number of mature oocytes, successful fertilization following an ICSI and satisfactory implantation rates might be possible contributing factors to acceptable live births. Further randomized controlled trials of patients with

different sizes of endometriomas would be needed to confirm our conclusions.

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