Oocyte accumulation for fertility preservation in women with benign ovarian tumours with a history of previous surgery, multiple or large cysts

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Oocyte accumulation for Fertility Preservation in women with benign ovarian tumors (BOT) with history of previous surgery or multiple/large cysts.

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ABSTRACT

Research Question: The study aimed to evaluate the relevance and the acceptance of an oocyte accumulation program in young women with benign ovarian tumor.

Design: This is a retrospective cohort study carried out in the Academic ART and Fertility Preservation Centre of the Lille University Hospital from January 2016 to December 2019. We evaluate the number of metaphase II oocytes per cycle and per patient after accumulation. We distinguished two groups for the analysis: endometrioma ("endometrioma") and dermoid, mucinous or serous cyst (« other cysts »).

Result(s): 113 FP cycles were analysed in 70 women aged 27.9±4.8 years. Almost all women had previous ovarian surgery before FP (89%). Mean AMH levels before COH was 12.5±8.7 pmol/L. 6.4±3.4 total oocytes were retrieved and 4.3±3.4 MII oocytes were vitirified per cycle. All agreed in to the oocyte accumulation program and all underwent at least 1 cycle. To date, 36 (51%) patients achieved 2 or 3 FP cycles. After accumulation,7.0±5.23 MII oocytes were vitrified per patient. No difference was found in terms of ovarian response and oocytes cohort between "endometrioma" and "other cysts" groups. Questionnaires after oocyte retrieval revealed abdominal bloating and mild pelvic pain in most patients with no difference according to the type of cyst. No serious adverse events occurred.

Conclusion(s): Oocyte accumulation should be systematically offered in young women with BOT whatever the histological type as it appears to be well-tolerated. Long-term follow-up is needed in order to assess the efficiency in terms of further pregnancy chances.

Key words: fertility preservation, oocyte vitrification, endometriomas, benign ovarian tumors.

Key message: Oocyte accumulation is needed to optimize the number of MII oocytes and further chances of pregnancy. FP procedures should be proposed in case of BOT, whatever the histological type.

INTRODUCTION

Ovarian cysts are observed in 10 to 20% of young women (American College of Obstetricians and Gynecologists 2007; Royal College of Obstetricians and Gynaecologists 2011; Raiga et al. 2006). 25% of them are organic cysts of which 25-35% are serous cystadenoma, 10-15% mucinous cystadenoma, 20% dermoid cyst and 20% endometrioma (American College of Obstetricians and Gynecologists 2007; Royal College of Obstetricians and Gynaecologists 2011; Raiga et al. 2006). In case of large, symptomatic or progressive cysts, surgery is performed for histological examination and confirmation of benignity. Ovarian sparing surgery has become crucial for the management of ovarian tumors in children, adolescents and young women for fertility concerns. Nevertheless, the size of the tumor can be a limiting factor, as large tumors are more likely to induce oophorectomy (Legendre et al. 2014; Dunselman et al. 2014; Borghese et al. 2013; Roman et al. 2010). In addition, all these tumors, especially endometriomas (Guo 2009), are at high risk of recurrence with consequent repeat surgeries (Harada et al. 2013; Rogers, Allen, et Kives 2014; Ben-Ami et al. 2010) leading to the risk of ovarian reserve damages and further fertility impairments.

It is now well-established that AMH is the most reliable indicator to the ovarian follicular content (Dewailly et al. 2014). Studies of the consequences of ovarian surgery on the ovarian reserve are almost all performed in case of endometriomas. They highlighted a significant decrease of AMH levels as high as 30 to 50% after cystectomy for endometriomas (Edgardo Somigliana et al. 2012; Uncu et al. 2013; Streuli et al. 2012; Goodman et al. 2016). This decrease is maximal in cases of large tumors, bilateral tumors whatever the size, and low ovarian reserve before surgery (Goodman et al. 2016; Younis et al. 2019; Muzii et al. 2015; Coccia et al. 2011). Ovarian damages are related to the excision of healthy ovarian cortex and

potential vascular injury when cystectomy is performed (Alborzi et al. 2009; Matsuzaki et al. 2009). In case of endometriomas, it has been shown that folliculogenesis can also be impaired due to ovarian tissue inflammation with premature follicle recruitment, higher rate of follicular atresia and alteration of the number and quality of growing follicles (Kitajima et al. 2014). The impact of cystectomy in cases of cystadenomas or dermoid cysts is less obvious, except if oophorectomy is needed due to large tumor size (Rustamov et al. 2016; Mohamed et al. 2016).

Fertility preservation (FP) techniques are developing rapidly and must be systematically offered to women with high risk of ovarian reserve depletion. Oocyte vitrification is the first line option in the case of non-oncologic and non-emergency situations, according to the ESHRE-ASRM 2015 committee opinion (Martinez et al. 2017; Martinez 2017). It is now well established that oocyte cryopreservation is safe and efficient, with healthy babies born, thanks to the vitrification techniques (A Cobo et al. 2018; Ana Cobo et Diaz 2011; Glujovsky et al. 2014; Argyle, Harper, et Davies 2016; Noyes, Porcu, et Borini 2009; Ana Cobo et al. 2014; De Munck et Vajta 2017).

Debates are still ongoing about FP strategies especially in endometriosis (E. Somigliana et al. 2015; Donnez, García-Solares, et Dolmans 2018) and French guidelines have been recently published on this topic (C. Decanter et al. 2018). To date, there is no published data regarding oocyte vitrification for FP in case of dermoid, serous or mucinous cysts; and only three cohort studies have been published exclusively in patients with endometrioma (Ana Cobo et al. 2020; Raad et al. 2018; Kim et al. 2020).

Because of the paucity of literature, we aimed to evaluate the relevance of an oocyte accumulation program in young women with BOT at high risk of ovarian reserve depletion due to previous surgery or presence of multiple or large cysts. The primary endpoint was to

evaluate the number of metaphase II (MII) oocytes eligible for vitrification after controlled ovarian hyperstimulation (COH) per cycle and after accumulation. The second endpoint was to examine the tolerance and the acceptability of the procedures in this specific population.

MATERIALS and METHODS

Study design

This is a retrospective analysis of collected data in the French ART registry (JFIV). This observational study was monocentric carried out in the Academic ART and Fertility Preservation Centre of the Lille University Hospital from January 2016 to December 2019. Written informed consents for both oocyte retrieval and oocyte vitrification were obtained before each procedure. The study was approved by the local ethic committee (DEC20150715-0002).

Population

Seventy patients with BOT, of which 89% had previous ovarian surgery. Large number of women have had first surgeries in other centres and sometimes years before, during chilhood or adolescence. They were referred to our FP centre, because of a cyst recurrence, and/or before surgery by surgeons from the Lille University Hospital Centre.

Inclusion criteria were age 18 to 35, history of BOT (endometrioma, dermoid, serous or mucinous cysts) with high risk of ovarian depletion: multiple ovarian cysts, ovarian cyst larger than 5 cm of diameter, history of oophorectomy or recurrent surgeries, baseline reduced ovarian reserve. Patients had to have a social insurance and be able to give an informed consent.

Exclusion criteria were a diagnosis of borderline or malignant ovarian tumor, personal history of thrombo-embolic events, or undetectable AMH levels.

An ovarian reserve assessment was systematically carried out before COH by measuring the serum AMH level and determining the antral follicle count (AFC). AMH was measured using an automated AMH assay, Access Dxi (Beckman Coulter Immunotech®, Villepinte France). The baseline AFC was measured with a Voluson E8 Expert (General Electric Systems,VELIZY, France) with a 5–9 MHz transvaginal transducer by counting all the 2–9mm diameter follicles.

Up to three vitrification cycles were offered to optimize the number of MII oocytes and further chances of pregnancy (A Cobo et al. 2018).

Controlled Ovarian Hyperstimulation (COH) protocol

Agonist or antagonist protocols were used for COH. Starting r-FSH dose was determined according to patient age, body mass index (BMI) and baseline AFC and AMH, and varied from 112.5 to 450 IU/day.

In 88,5 % of cases, we used the fixed day 6 antagonist protocol. COH was initiated on Day 2 of a spontaneous bleed. Recombinant FSH (Follitropin alpha, Gonal F®**,** Merck-Serono, or Follitropin beta, Puregon®**,** Merck USA) was administered daily until triggering and GnRh antagonist (Ganirelix, Orgalutran® 0.25mg/0.5ml MSD) was added daily on day 6. Transvaginal ultrasound examination combined with estradiol and LH measurements were performed to monitor the follicles development on day 6 of r-FSH treatment and every 2 or 3 days after.

For the long GnRH agonist protocol, the GnRH agonist (Nafaréline, Synarel® 0.2mg/dose, pfizer) was initiated during the luteal phase of the previous cycle for pituitary down-regulation. After ultrasound examination and hormone levels measurement, r-FSH and GnRH agonist were administrated daily following the instructions previously described.

Triggering was achieved as soon as three follicles reached 18 mm of diameter or larger by

administering hCG (250 µg, Ovitrelle ®, Merck Serono) or by 0.2mg triptorelin (Decapeptyl ® Ipsen Pharma) for patients with high risk of ovarian hyperstimulation syndrome in case of antagonist protocol (Youssef et al. 2014).

Oocyte retrieval

Oocyte retrieval was scheduled 36 to 38 hours after triggering and was performed by transvaginal ultra-sound guided needle aspiration. Two hours after oocyte retrieval, cumulus oophorus was denuded by a brief exposure to 80 IU/mL of hyaluronidase solution (Hyaluronidase Fertipro™, Belgium) followed by mechanical removal of the corona radiata with denudation pipette (Flexipet, Cook, USA) in a controlled CO2 and temperature environment. Oocyte vitrification procedure was carried out after nuclear maturity assessment under stereomicroscop. Only MII oocytes were eligible for vitrification procedure.

Vitrification protocol

We used the RapidVit Kit® (Vitrolife®, Sweden) and the closed system device RapidI® (Vitrolife®, Sweden). Vitrification procedure was performed as previously described (Christine Decanter et al. 2018). Briefly, oocytes were exposed to progressive concentrations of propanediol and ethylene glycol. Oocytes were loaded on the RapidI device in a minimum volume drop and immediately plunged into liquid nitrogen to induce vitrification and then stored at -196°C in liquid nitrogen

Questionnaire

In accordance with our ART center policy, each patient was called back after the oocyte retrieval to answer a questionnaire regarding tolerance. They were also asked about symptoms of pelvic pain, abdominal bloating and fever. Pain intensity was assessed using a self-report scale from 0 to 10 (Numerical Scale, Echelle Numérique: EN). We have classified them into 3 categories: low intensity pain (EN≤3), medium intensity pain (4≤EN≤6) and high intensity

pain (EN≥7).

Statistical analysis

Categorical parameters were described as frequencies and percentages. Continuous parameters were described as means and standard deviations.

A generalized estimating equation (GEE) model (Poisson distribution and logit link function) taking into account the correlation between the cycles of a same patient was used to assess the associated factors with the number of MII oocytes. In the case of p-value lower than 0.10 in univariate analysis, the parameter was introduced in a multivariate model.

The comparison between « endometrioma » vs « other cysts » groups were performed using Chi-square test for « patient level » categorical variables, using Student t-test for « patient level » continuous variables. For « cycle level » variables, a linear mixed model with « patient » as random effect was used for dependent continuous variables; a GEE model like previously quoted for dependent count variables.

Data were analyzed using the SAS software (SAS Institute Inc, Cary, NC, USA) and all statistical tests were performed with a 2-tailed alpha risk of 0.05.

RESULTS

Population characteristics

70 patients were referred to the Fertility Preservation Centre of the Lille University Hospital. All agreed in to the oocyte accumulation program and all underwent at least 1 cycle. 51,4% of them underwent 2 cycles and only 10,0% underwent 3 cycles.

Distribution of the different histological types of BOT in the study population is represented in Figure 1: endometrioma (n=39, [56%]), dermoid cyst (n=22, [31%]), mucinous cyst (n=5, [7%]), and serous cyst (n=4, [6%]). We distinguished 2 groups in the overall population so-called “endometrioma” (n= 39) and”other cysts” (n= 31) including dermoid, serous and mucinous cysts.

89% (n=62) of patients had a history of ovarian surgery prior to FP: cystectomy (n=36 [58%]), plasma energy ablation (n=1 [2%]), drainage (n=7 [11%]), unilateral oophorectomy (n=18 [29%]). Among these patients, 33 had a cyst recurrence of which 15 underwent a second surgery: 8 had a cystectomy on the contralateral ovary after oophorectomy, 3 had a second cystectomy and 4 had drainage secondary to a cystectomy (supplemental figure 1). 8 patients (11%) were included prior to surgical management. 32 patients (45.7 %) had a cyst during the stimulation period.

Characteristics of the patients are reported in Table 1. Mean age at accumulation program proposal was 27.9±4.8 years. The average diameter of largest cyst was 7.4 ± 4.2cm (7.9 ± 4.2cm in women with previous surgery and 3.8 ± 2.0cm in women with no history of surgery). Mean AMH levels was 12.5±8.7 pmol/L and AFC was 13.1±7.9 follicles. Twenty-nine patients (41.4%) had already low AMH levels, between 3 and 8 pmol/L, the latter being

our in-house threshold for predicting poor ovarian response. Thirty-six patients (51.4%) were taking oral contraceptive pill (n=32) or long agonist GnRH (n=4) before COH.

COH outcomes and oocyte cohort

Main COH outcomes are detailed in Table 2. A mean of 6.4±3.4 total oocytes was retrieved per cycle. The mean number of MII oocytes was 4.3±3.4 per cycle and of immature oocytes was 0.6±1.0 (germinal vesicle and immature metaphase I oocyte). Maturation rate was of 66%. In 41.5% of cycles, four or fewer total oocytes were retrieved.

In the overall population the mean number of MII oocytes was 7.0±5.2 per patients after accumulation. 44.3% of them (n=31) had more than eight MII oocytes vitrified. A mean number of 4.2±3.4 MII oocytes was vitrified at the end of the first cycle, 8.0±5.4 after two cycles and 9.4±5.6 after three cycles (Table 2). After 1 cycle, only 15.7% of patients had 8 or more MII oocytes eligible for vitrification. After 2 or 3 cycles, 52.8% to 57.1% had more than 8 MII oocytes eligible for vitrification. In 5 patients, no oocyte was eligible for vitrification after one (n=3) or two cycles (n=2). 3 of them had endometriomas, the others had dermoid and mucinous cysts. They did not have any particular characteristics at baseline and during COH. Their AMH levels were 3 pmol/L to 17.7 pmol/L.

Associated factors with the number of MII oocytes

Univariate analysis showed that AMH level (RR 1.38, 95%CI [1.17-1.62]), AFC (RR 1.40, 95%CI [1.23-1.59]), estradiol level at triggering day (RR 1.19, 95%CI [1.08-1.33]) and the number of mature follicles ≥15 mm (RR 1.09, 95%CI [1.05-1.14]), had a significant positive impact on the number of MII oocytes ($p<0.05$). Conversely, BMI (RR 0.96, 95%CI [0.93-0.98]), history of oophorectomy (RR 0.65, 95%CI [0.47-0.88]), r-FSH starting dose (RR 0.72, 95%CI [0.60-0.83]) and r-FSH total dose (RR 0.87, 95%CI [0.79-0.96]) were negatively associated with the number of MII oocytes ($p<0.05$). There was no effect of smoking,

histological type, age, taking oral contraceptive pill (OCP) before COH on the number of MII oocytes.

In the multivariate analysis, only the r-FSH starting dose, estradiol level and number of mature follicles ≥ 15 mm at triggering day remained significantly associated with the number of MII oocytes (respectively, RR[95%CI], 0.80 [0.67-0.95], p=0.012; 1.10 [1.01-1.21], p=0.032; 1.06 [1.01-1.11], p=0.009).

« Endometrioma » versus « other cysts»

We compared the two subgroups "Endometrioma" and "other cysts" (table 3). Patients with dermoid or sero-mucinous cysts were significantly younger and had a higher incidence of unilateral oophorectomy. There was no difference between the 2 groups at baseline regarding ovarian reserve indicators, smoking, BMI and taking OCP. No difference was found regarding the follicular growth under COH, neither total and MII oocytes number between the 2 groups.

Follow-up

Only one case of moderate ovarian hyperstimulation syndrome was reported. No infection, hemorrhagic or thromboembolic complications occurred. 100% of patients completed the questionnaire after each cycle. Questionnaires after oocyte retrieval (n=113) revealed abdominal bloating and mild pelvic pain in most patients (figure 2). There was no difference according to the type of cyst.

To date, 3 patients asked for reutilization. A total of 8 MII oocytes were thawed and resulted in one live birth of a healthy baby.

DISCUSSION

To date, this is the first cohort study interested in a systematic proposal of oocyte accumulation for FP in case of BOT whatever the histological type. These results confirmed those we previously showed in a short series of patients (Dadoun et al. 2017). Only three retrospective cohort studies have been published since on this topic but exclusively in women with endometrosis (Raad et al. 2018; Ana Cobo et al. 2020; Kim et al. 2020). Cobo *et al*. reported the results of 840 cycles performed in 485 women in their thirties, Raad *et al*. 70 cycles in 49 women of same age, and Kim et al 50 cycles in 34 women before surgery with a mean number of MII oocytes per cycle of 7.2, 5.5 and 4.8 respectively (Ana Cobo et al. 2020; Raad et al. 2018; Kim et al. 2020). We reported in our overall population a mean number of 4.3 MII oocytes eligible for vitrification per cycle and a mean number of 7.0 MII oocytes per patients after accumulation. These results are slightly lower than those found by Cobo *et al* and Raad *et al* despite a younger population. It must be stressed that in these two series, every types and stages of endometriosis were eligible for FP, including women with superficial lesions, absence of endometrioma or previous surgery. However, our results were similar to those of Kim et al. in patients without history of surgery. In the current study, we voluntarily focused on young patients under 35 years with high risk of ovarian function impairment due to history of repeated surgeries and/or presence of multiple or large ovarian tumors. Indeed, in our population, 89% had at least one previous ovarian surgery of which 26% had an oophorectomy, in comparison with 47% and 38% in Cobo and Raad Serie (Ana Cobo et al. 2020; Raad et al. 2018). The latter reported fewer retrieved oocytes in these “post-surgery” patients, which is in agreement with our results. This is in accordance with the literature reporting ovarian damage after cystectomy for endometrioma (Edgardo Somigliana et al. 2012; Uncu et al. 2013; Streuli et al. 2012; Goodman et al. 2016), but also for serous,

mucinous and dermoid cysts (Rustamov et al. 2016; Mohamed et al. 2016). Unfortunately, lot of patients, especially in this cohort, had their first surgeries in other centres and sometimes years before, explaining the high proportion of patients with a history of cystectomy or oophorectomy in our cohort. Surgery withhold in cases with endometrioma should be discussed and excision should be cautiously considered. Conservative treatment should be counselled as the first line of treatment, until the patient's reproductive aspirations are realized.

In keeping with the high incidence of previous surgery, our patients already had an impairment of their ovarian reserve: they indeed exhibited lower AMH levels than expected with a mean of 12.5±8.7 pmol/L, i-e, <-1 Standard Deviation for age (Kelsey et al. 2011). 41.4% of them had an AMH level lower to 8 pmol/l that represents our in-house cut-off threshold for predicting poor ovarian response. This indicates that these patients should have been referred to a FP centre earlier, ideally before surgery, to have more MII oocytes. Half of the population had been using OCP for at least 6 months which may have influenced the basal AMH levels (Kallio et al. 2013; Hagen et al. 2012). Nevertheless, COH while using OCP did not impact the ovarian response nor the number of MII oocytes. Interestingly, AMH levels in the multivariate analysis was no longer associated with the number of MII oocytes. In addition, if we consider results in terms of oocyte number patient by patient, a significant part (47%) with low or very low AMH levels had more than 4 total oocytes retrieved. This confirms that low AMH levels should not be an exclusion criterion before COH for FP in young patients. Maturation rate in our population of BOT was lower than expected in comparison with maturation rate in women undergoing FP for social reasons (A Cobo et al. 2018; Garcia-Velasco et al. 2013; Rodriguez-Wallberg et al. 2019), and in ICSI patients in our centre (Christine Decanter et al. 2018). It has to be noted that 45,7 % of our patients had an ovarian tumor during the ovarian stimulation. One can hypothesize the existence of follicular

micro-environment alterations impacting the oocyte development and maturation, as it was described in case of endometriomas due to chronic inflammation (Singh et al. 2016; Sanchez et al. 2017) and in oncologic indications (Christine Decanter et al. 2018).

Patients from "other cysts" group were younger and had a higher incidence of oophorectomy than those in "endometrioma" group. Nevertheless, there was no statistical difference between the 2 groups regarding the follicular growth under COH and the oocyte cohort in terms of number and quality. Early referral of these young patients is recommended in order to prevent a possible risk of recurrence which would have a greater impact on their future fertility. Nevertheless, whether FP strategies should be the same in these two groups, this remains to be established in larger prospective series.

Rienzi *et al*. and Cobo *et al*. showed in different populations, i.e ICSI, oocyte donation or oocyte vitrification for social reasons, that the best chances of pregnancy are observed when oocyte collection is performed under 35 years old (A Cobo et al. 2018; Rienzi et al. 2012; Ana Cobo et al. 2016). They indeed reported in this age range that 8 MII oocytes may provide 30 to 45% of cumulative live birth rate (A Cobo et al. 2018; Rienzi et al. 2012; Ana Cobo et al. 2016). The younger the patient, the better her chances of being pregnant. In our subgroup patients with a history of recurrent surgery, the mean number of MII oocytes was too low after one cycle. Oocyte accumulation concept was primarily proposed by Cobo *et al.* in patient with low ovarian reserve in IVF procedure to increase pregnancy chances (A. Cobo et al. 2012) and is now routinely proposed in case of FP. Only 4.3±3.4 MII oocytes were vitrified per cycle in this study which clearly does not insure pregnancy achievement justifying the accumulation program. We indeed observed in our population a clear increase in the number of MII oocytes after accumulation, as also suggested in the cohort of Kim et al (Kim et al. 2020). Hence, if we extrapolate the recent results of Cobo *et al*. to our patients , aged of 28, with a mean number of 7.0 MII oocytes after accumulation, they may have 30%

chances of live birth rate (A Cobo et al. 2018). But, it has to be stressed that these results concerned patients in an elective FP program. In the FP series in women with endometriosis, Cobo *et al* showed a cumulative live birth rate of 46,4% with an average of 9 MII oocytes per patient (Ana Cobo et al. 2020).

The acceptability of FP by oocyte vitrification was high as all patients agreed the procedure at the time of offer. But it is interesting to note that only 51.4% of them returned for a second cycle and 10.0% for a third one, even though in France, FP for medical reasons is completely supported by social insurance without any advance of costs. In addition, no severe adverse event occurred, and the functional tolerance was good. Logistical difficulties, and disappointment regarding the oocyte number at the first cycle were the main reasons for not coming back.

The retrospective design of this study with a limited number of patients does not allow us to preclude firm conclusions. Nevertheless, we analysed data prospectively collected extracted from our ART national registry, allowing us to have exhaustive and precise population description.

It is now too soon to evaluate the efficiency of these procedure on further fertility as only 3 patients asked for re-utilization. Large prospective studies with a long-term follow-up are clearly needed to estimate the re-utilization rate, the oocyte quality through fertilization and further pregnancy rates.

To summarize, the results of this study highlighted that in this population of patients with history of surgeries and/or multiple or large cysts, oocyte accumulation is needed to optimize the number of MII oocytes and further chances of pregnancy. FP procedures should be offered in case of BOT, whatever the histological type, ideally before the ovarian surgery if it is technically feasible. Fertility sparing surgery remains the most challenging option in these young women until the patient's reproductive aspirations are realized.

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LEGENDS of FIGURES

Figure 1: histological types of BOT

Figure 2: Tolerance questionnaire result

Table 1 : Population characteristics	
Characteristics	**Values (n = 70)**
Age (years)	27.9±4.8 *28.0 [18.0-35.0]*
Smoking [a]	23/70 (33.3)
Ovaries number	
1	18/70 (25.7)
2	52/70 (74.3)
Mean number of surgeries	1.2±0.75 1.0 [0-2.0]
Diameter of largest cyst (cm)	7.4 ± 4.2 *6.8 [2.0-20.0]*
Contraception	
No	34/70 (48.6)
Yes	36/70 (51.4)
Number of FP cycles	
1	34/70 (48.6)
2	29/70 (41.4)
3	7/70 (10.0)
Body Mass Index (kg/m²)	24.3±5.6 *22.9 [17.0-42.7]*
Total AFC	13.1±7.9 *12.0 [4.0-36.0]*
AMH (pmol/L)	12.5±8.7 *9.6 [3.0-43.0]*
AMH ≤ 8 pmol/L	29/70 (41.4)

Values are expressed as mean ± standard deviation and median [mini-maxi], or number (percentage).

[a] 1 missing data

Table 2 : COH outcomes	
Parameters per cycle (n=113)	**Value**
Protocol antagonist agonist	 100/113 (88.5) 13/113 (11.5)
Recombinant FSH starting dose (UI)	306.5±101.6 *300.0 [112.5-450.0]*
Recombinant FSH cumulative dose (UI)	3319±1441 *3000 [675.0-9000]*
Duration of ovarian stimulmation (days)	10.6±2.1 *10.0 [5.0-18.0]*
Oestradiol level at triggering day (ng/ml)	1270±1088 *874.0 [173.0-6654]*
Triggering hCG (250 µg, Ovitrelle) 0.2 mg triptorelin	 101/113 (89.4) 12/113 (10.6)
Number of follicles ≥15mm	6.4±3.4 *6.0 [1.0-19.0]*
Number of MII oocytes	4.3 ± 3.4 *6.0 [0-19.0]*
Number of MII oocytes/ Total oocytes : maturation rate	482/724 (66.6)
Number of MII oocytes/ Number of follicles ≥ 15mm	0.7 ± 0.6 *0.7 [0-2.5]*
Low ovarian response ≤ 4 total oocytes	47/113 (41.5)
Parameters per patient (n=70)	
Number of MII oocytes / patient after accumulation	7.0 ± 5.2 *6.0 [0-22.0]*
Number of MII oocytes after 1 cycle	4.2 ± 3.4 *3.0 [0-16.0]*
Number of MII oocytes after 2 cycles	8.0 ± 5.4 *9.0 [0-22.0]*
Number of MII oocytes after 3 cycles	9.4 ± 5.6 *9.0 [3.0-18.0]*
≥ 8 MII oocytes	31/70 (44.3)

Values are expressed as mean ± standard deviation and median [mini-maxi], or number (percentage)

Table 3 : Comparison « endometrioma » versus « other cysts »

	Other N=31	Endometrioma N=39	p value
Age (years)	25.8±4.4	29.5±4.6	0,001
Smoking	12 (40)	11 (28.2)	0.30
Ovaries number :			
1	16 (51.6)	2 (5.1)	0.001
2	15 (48.4)	37 (94.9)	
BMI (kg/m²)	24.6±6	24.2±5.5	0.77
AMH (pmol/L)	12.7±9	12.3±8.5	0.85
AFC	13.6±7.6	12.8±8.2	0.73
Contraception :			
Yes	13 (41.9)	23 (59.0)	0.16
No	18 (58.1)	16 (41.0)	
r-FSH starting dose [a]	309.2±97.7	304.5±105.3	0.78
r-FSH cumulative dose [a]	3597±1725	3105±1149	0,097
Duration of ovarian stimulation [a]	10.9±2.3	10.3±1.9	0.17
E2 level at triggering day [a]	1139±1167	1369±1021	0.18
Number of follicle ≥ 15mm [a]	6.8±4,0	6.0±2.8	0.25
Total oocytes [a]	7.3±4.9	5.8±3.8	0.11
MII oocytes[a]	4.8±3.9	3.9±3.1	0.18
Maturation rate [a]	233/356 (65.4)	249/368 (67.7)	0.58

Values are expressed as mean ± standard deviation or number (percentage)

[a] Values are calculated over all cycles (n=49 cycles for « other » group, n=64 cycles for « endometrioma »).

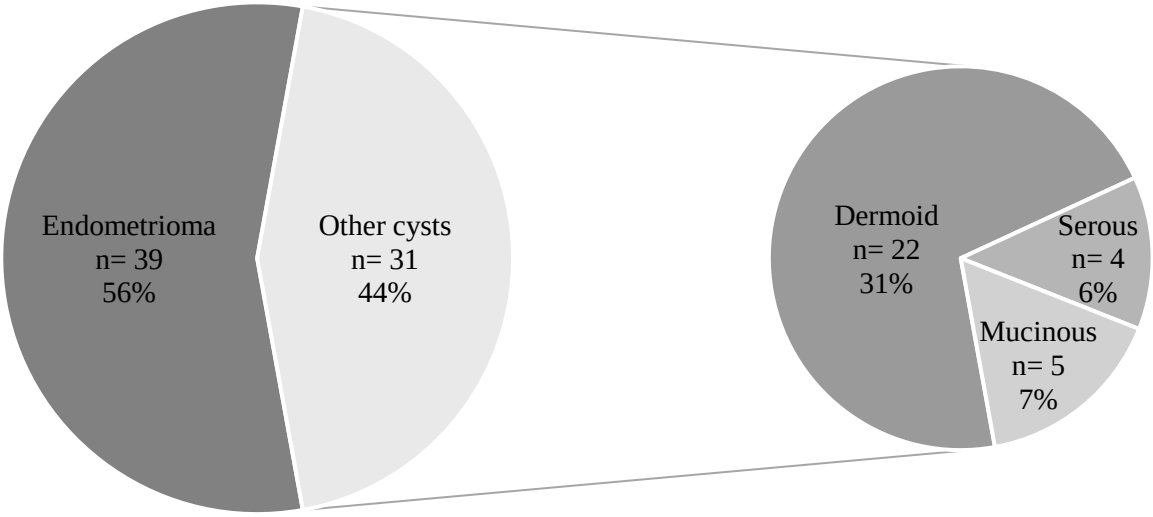
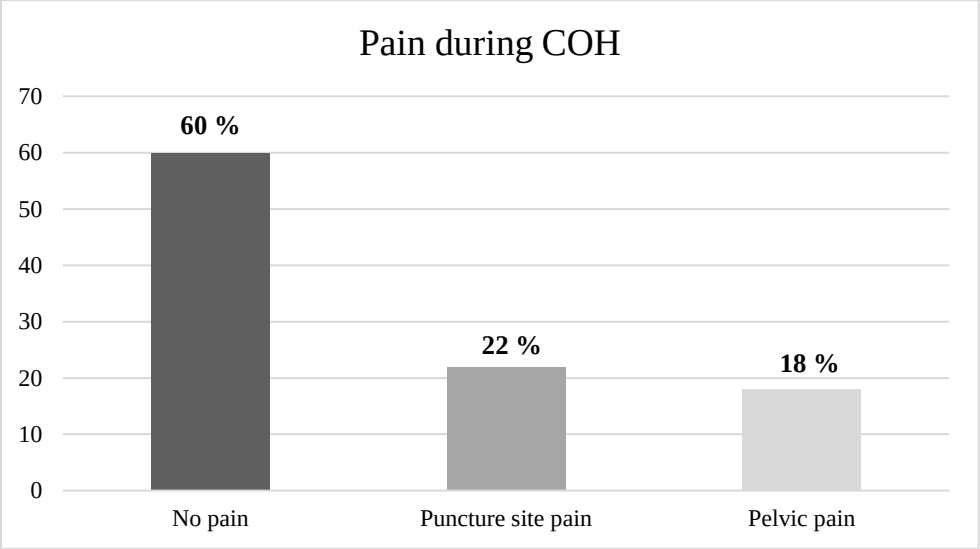
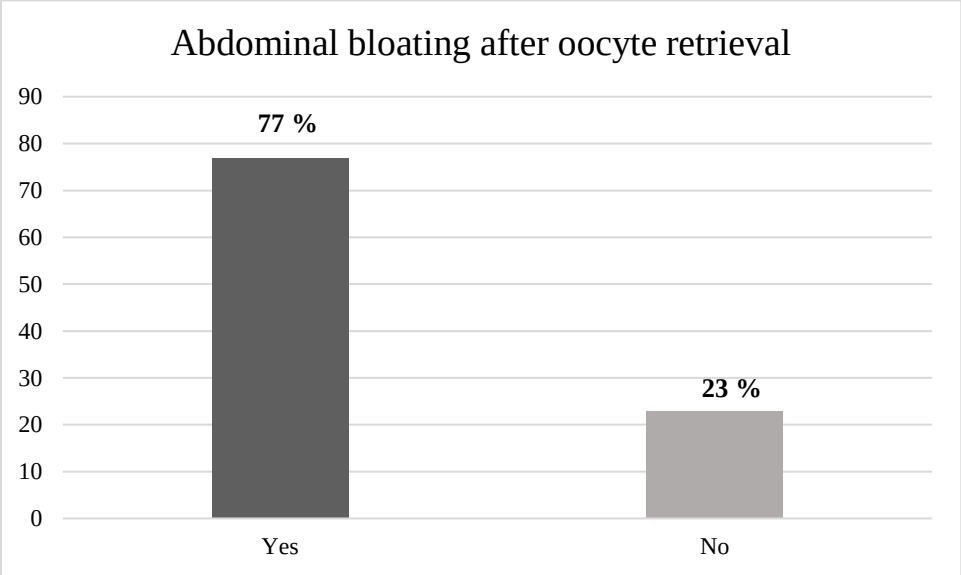
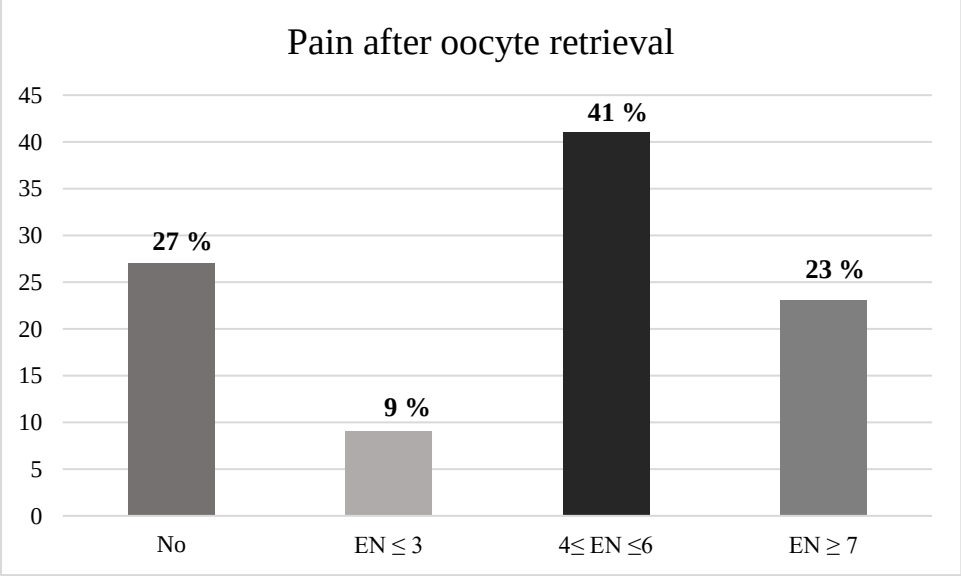

Endometrioma
n= 39
56%
Other cysts
n= 31
44%
Dermoid
n= 22
31%
Serous
n= 4
6%
Mucinous
n= 5
7%

Figure 1







EN ≤3: low intensity pain,

4≤ EN ≤6: medium intensity pain,

EN ≥7: high intensity pain

Figure 2