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Abstract

Objective: We aim to evaluate the knowledge and physicians' practices concerning fertility preservation in women with endometriosis.

Design: Descriptive, observational, national study using an online self-questionnaire, sent by email to French gynaecologists in October 2019 within 2 months.

Results: We obtained 110 analyzable responses from mainly surgeons (54%) and reproductive clinicians (19%) with a good experience (average 15 years of practice). Amongst these practitioners, 91% seemed aware of latest French recommendations on endometriosis issued in December 2017. The most commonly used surgical techniques for management of endometriomas were intra-peritoneal cystectomy (51%), vaporization by plasma energy (29%) and destruction by bipolar coagulation (8.5%). Preoperative AMH was systematically or often prescribed by 78% of the practitioners against 37.3% who did it postoperatively. Furthermore, 74% also considered and performed fertility preservation strategy to manage endometriosis. It was offered in situations of bilateral or recurrent endometrioma, but only 33% offered it in unilateral endometrioma cases. In the cases recorded, vitrification of mature oocytes appears to be the most common fertility preservation technique (used by 87% of the practitioners).

Conclusion: We observed in our population of sensitized practitioners a good and adequate knowledge concerning endometriosis physiopathology and recommendations for its management, with good information delivery to women. Operating techniques are adapted although information and education concerning fertility preservation indications seem necessary. The place of multidisciplinary concertation meeting in endometriosis appears essential both for discussion of

surgical indications and for fertility preservation possibilities. Creation of dedicated structures should be encouraged.

Keywords

physicians' practice, fertility preservation, endometriosis

Abbreviations

AFS: American Fertility Society

AMH: Anti-Mullerian Hormone

CNGOF: French College of Gynaecologists and Obstetricians

FP: Fertility Preservation

HAS: French National Authority for Health

IVF: In Vitro Fertilization

OR: Ovarian Reserve

PFO: Premature Ovarian Failure

SCGP: Society of Gynecological and Pelvic Surgery

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Introduction

According to French law, "any person whose medical care is likely to impair fertility, or whose fertility is likely to be prematurely impaired, may benefit from collection and conservation of gametes or germinal tissues, and may benefit from assisted reproductive technology for restoration of fertility". Initially developed to be performed prior to cancer treatment, fertility preservation (FP) has now been extended to benign indications: autoimmune diseases treated with gonadotoxic agents, risk of premature ovarian failure, etc… The most commonly used techniques are: vitrification of mature oocytes after controlled ovarian hyperstimulation and cryopreservation of ovarian tissue after oophorectomy by laparoscopy.

Endometriosis is a common benign gynecological condition affecting about one in ten women [1]. It is often associated with infertility [2]. Though the cause-effect relationship remains controversial, the etiology of infertility may lay within the manifestation of endometriosis itself; tubal obstruction secondary to adhesions, chronic pelvic inflammation responsible for impairment of tubal ciliary action [3], endometrial receptivity disorder, reduction in ovarian reserve [4]; and surgical treatment of endometriosis is furthermore likely to have a negative impact on the follicular capital. Affected patients are therefore potential candidates for fertility preservation.

The aim of our study was to evaluate the knowledge and physicians' practices of French gynaecologists concerning FP in women with endometriosis.

Materials and Methods

We carried out a descriptive, observational, national study. An evaluation by self-questionnaire, available online (https://docs.google.com/forms/d/1UE-

5cGBB77h4WrKLXrfWEoGCa7eSTwut76qWDVm3JGk/prefill) was distributed by e-mail via different societies, including the Society of Gynecological and Pelvic Surgery (SCGP) and the French College of Gynaecologists and Obstetricians (CNGOF) between October and December 2019. Participation was voluntary, unpaid and anonymous. The guidelines of the French College of Gynaecologists and Obstetricians (CNGOF) and the French National Authority for Health (HAS) issued in December 2017, were used as reference to evaluate the clinical practices [5]. The data was collected using Google Form and statistical analysis performed by Google Sheet. Qualitative variables were expressed as numbers and percentages, and quantitative variables as means ± standard deviation.

Results

We collected 110 analyzable responses. The socio-demographic characteristics of our respondents are presented in Table 1.

Clinical practice and training: Almost all of our population of gynecologists (98%, n=108) had patients with endometriosis with an estimated number of consultations of 122 ± 161 [2-800] per year. Among those who answered our questionnaire, 91% (n=100) seemed aware of latest recommendations. We have highlighted that more than a third of the practitioners (37%, n=41) had never received specific training on FP in endometriosis.

Knowledge of endometriosis: Global prevalence of endometriosis (10%) amongst women of reproduction age was correctly estimated by 70% (n=77) of our sampled practitioners. All (100%) considered endometriosis to be a factor of infertility and 91% (n=100) knew that it was not systematically pathological. Practitioners stated that diagnosis was mainly clinical (68%, n=75) and/or histological (70%, n=77).

Practices concerning fertility: Our findings revealed that 75% (n=83) reported that patients discussion about their fertility occurred “systematically” and 22% (n=24) described these to occur "often". In addition, 29% (n=32) of the practitioners also reported that women spontaneously and frequently discussed the impact and consideration for FP.

Surgical management: Figure 1 shows the most commonly used surgical techniques for management of endometriosis cysts: 51% performed intra-peritoneal cystectomy by "stripping" or divergent traction, 29% vaporization by plasma energy and 8.5% destruction by bipolar coagulation.

Surgeons in our cohort operated about 57 ± 69 [0-300] patients with endometriosis every year. Amongst our cohort, 64% (n=38) systematically indicated an AFS (American Fertility Society) score in their operation report. For 47.5% (n=28), prescription of Anti-Mullerian Hormone (AMH) dosage in preoperative care was systematic whilst 30.5% (n=18) often prescribed it. Only 37.3% (n=22) prescribed it systematically or often in a postoperative setting: 70% prescribed AMH at 3 months and 22% at 6 months. A medical treatment in post-operative period to suppress ovarian activity was prescribed by 88% (n=52) of the surgeons, of which oestroprogestative contraception was the preferred option for 59% (n=35) of them.

Fertility preservation practices: Practitioners worked in collaboration with a dedicated center for 90% (n=99) of them. Almost 75% (n=81) had already performed FP for endometriosis. The situations in which they offered it are presented in Table 2. The main inclusion parameter for FP decision was age (98%, n=85). The most commonly performed technique was vitrification of mature oocytes in 87% (n=58).

Discussion

To the best of our knowledge, this is the first study about physicians' practice patterns in the diagnosis and management of endometriosis.

The results show that the physiopathology of endometriosis and recommendations for its management, including FP were well known in the population of 110 practitioners who participated in our study. They often communicate the management strategies and address patients' expectations. They seem to deliver clear information about the opportunity of FP in most cases (75%), facing a population particularly well-aware and sensitized.

Preferentially performed operative techniques for the management of endometriomas by our sub-population of surgeons were: intra-peritoneal cystectomy, which is the reference treatment [5] and vaporization by plasma energy, the latter being potentially less harmful for the ovarian reserve (OR) at the cost of a higher number of recurrences of endometriomas [6-8]. Destruction by bipolar coagulation was still used, although it is no longer recommended [5].

An average of 57 patients per year was operated by each surgeon. The surgical level of expertise has previously been inversely correlated with the amount of healthy ovarian tissue removed during cystectomy [9-10]. Therefore "expert surgeons" in regional reference center [11] may be preferred for operations of patients with endometriosis. A national working group is currently dedicated to the creation of such structures on French territory.

Staging of rAFS [12] is not compulsory, and a third of our surgeons did not notify it in their operative report. Its use is nevertheless encouraged in order to facilitate

exchanges between professionals. AFS score can be integrated into the EFI score (endometriosis fertility index) [13], in order to adapt the treatment.

The adverse effects of removal of endometriomas are increasingly clear and AMH pre and post-surgery is a useful marker in assessing the degree of damage to the ovary.

In our analysis, it emerged that an evaluation of the OR, reliably predicted by a preoperative AMH measurement, was prescribed by only half of our surgeons.

Preoperative measurements can detect any alteration of OR which may be attributable to the disease. Moreover, ovarian cystectomy presents a risk, adversely impacting the follicular capital by removal or destruction of the healthy parenchyma surrounding the cyst, resulting in a significant reduction in post-operative AMH [14-16]. This risk seems to be higher in cases of endometriomas compared with other benign cysts [17], as well as in patients undergoing iterative interventions [18]. Bilateral surgery in patients may also trigger earlier menopause (42 years) and a higher incidence of premature ovarian failure (PFO) [19]. Finally, when facing an operation for severe endometriosis without planned cystectomy, knowledge of low preoperative AMH could guide the surgeon who will adapt his gesture in order to limit excessively large peri-ovarian dissections.

A limited number of physicians (37.3%) integrated AMH dosage in post-operative care. Although it is not part of the recommendations, it is interesting to assess the impact of the intervention on OR. There is a significant reduction in OR during the immediate post-cystectomy period [14-16], which could be explained by the unintentional removal of ovarian cortex surrounding the cyst. Medium-term influence of cystectomy on OR might be attributed to vascular compromise resulting from

excessive electrosurgical coagulation and postsurgical inflammation. A recovery of OR is possible with a variable capacity according to studies (Table 3). It can be explained by a favorable healing process with ovarian reperfusion [21] or a follicular cohort rearrangement [24]. It is thus difficult to predict the proper time to offer this control but it could be advisable not to dose AMH too early after cystectomy, not before 3 months at least. The majority (70%) of our surgeons prescribed it at that time.

Our cohort (88%) applies the prescription of a medical treatment in post-operative period, such as oestroprogestative contraception, in accordance with the recommendations [5], in order to reduce the risk of recurrence of endometriomas.

Our sample of experienced physicians appropriately applies recommendations for fertility preservation [26] in situations in which a systematic proposal should be made, such as bilateral endometriomas (77%) or recurrent endometriomas (96%) but only a few do so in cases of unilateral endometrioma (33%). Currently, fertility preservation is recommended facing endometriomas measuring ≥ 5 cm. Therefore efforts to increase awareness needs to be implemented.

Gynecologists also include FP in the management of isolated deep endometriosis in patients with reduced AMH (87%). However, there is no real framework for this situation and it should be discussed on a case-by-case basis according to age, marital status, OR, progressive nature of the lesions and the likelihood of using IVF techniques [26].

Although FP is included in endometriosis management, there is no consensus in the international literature on strategies for FP in this context, and some indications may be very close to societal demands. In this sense, it seems essential to discuss the demands for FP during multidisciplinary, multisite, specialized consultation meetings dedicated to endometriosis with the presence of a reproductive physician.

Cryopreservation of mature oocytes, mostly performed (87%) by our cohort, is the reference technique [27], since it is reliable. Cryopreservation of embryos or ovarian tissue remains a possible alternative.

We still need to define the best timing to offer this FP program to our patients. A critical factor is age, correlated with oocyte quality. It remains to be the main parameter involved in the decisions made by our cohort of physicians (98%). Importantly, age also correlates with the rate of embryonic aneuploidy wherein it appears to be increasing (>40%) at both extremes: before 23 and after 36 years old in general population [28]. The clinical significance of aneuploidy is undoubted. Cobo et al [29] found that the probability of live birth for patients >36 years are halved compared to patients ≤35 years (19.9% vs 40.8%) when eight oocytes were used.

As such, evaluation of the benefit/risk ratio of this FP procedure should be extensively discussed beforehand. There is an inherent risk related to anesthesia, regardless of its mode during ovarian puncture but also a risk of post-puncture abscess that can reach 1.7% [30]. Encouragingly, the risk of a possible recurrence or increase in endometriosis-related pain by ovarian stimulation does not appear to be increased [31]. Also, the risk of ovarian hyperstimulation is normally ruled out by carrying out antagonist protocols, allowing for ovulation to be triggered by a GnRH

agonist. Nevertheless, the patient must be informed about risks, as well as the challenging pathway of the procedure, the possibility that several stimulation cycles may be necessary to achieve satisfactory egg accumulation and the low chance of reusing vitrified oocytes (9% in Cobo's study [29]).

One limitation of this study is the very low participation rate. Indeed, among 7865 gynecologists listed in France, we obtained only 110 answers. Practitioners who answered the questionnaire were those who were interested in endometriosis and who were dealing with the pathology for a long time (57 patients operated every year and 15 years of practice). This may explain their good knowledge and their sensitivity towards FP. Due to this major selection bias, our results cannot be extrapolated to the overall population of gynecologists in France.

Conclusion

In this study, among physicians responding to the questionnaire, we underlined good knowledge concerning endometriosis physiopathology and the associated risk of impaired fertility. Surgeons used appropriate operating techniques to preserve patients' ovarian prognosis but information and education concerning FP indications seemed necessary.

The place of multidisciplinary consultation meeting in endometriosis appears essential both for discussion of surgical indications and for FP possibilities. Creation of dedicated structures should be encouraged.

Fertility preservation must be carried out "neither too early nor too late" in order to achieve a significant chance of pregnancy for the patient later on. Nevertheless, it remains difficult to predict the risk of infertility in these patients with endometriosis,

with sometimes difficult situations close to societal FP. Finally, the possible cost to society is also an important parameter to take into account when setting up such a program, especially regarding the high frequency of endometriosis in general population.

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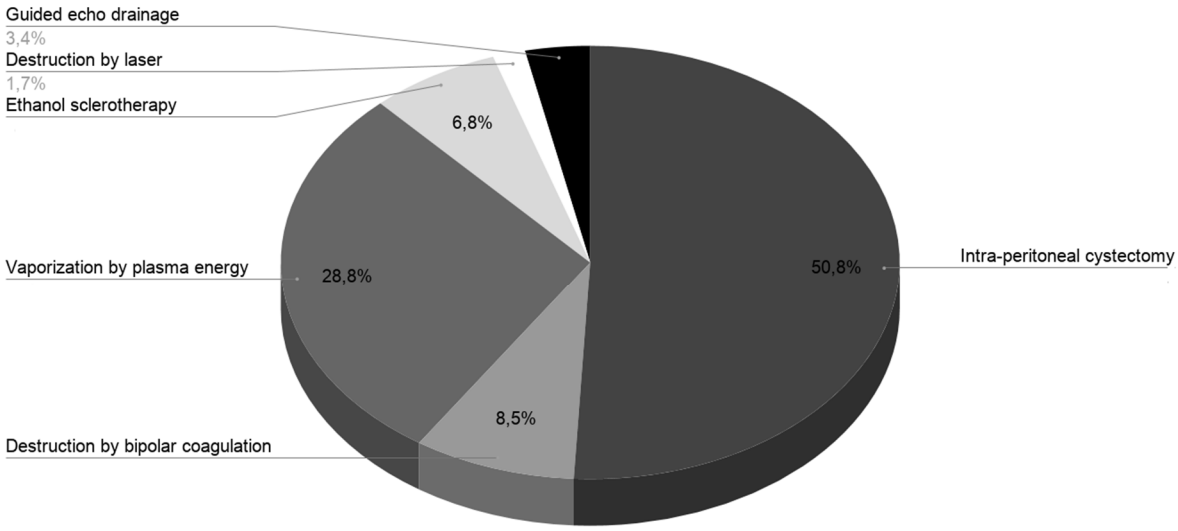

Figure 1: Most commonly used surgical technique for the management of endometriomas

Table 1: Socio-demographic characteristics of gynecologists answering questionnaire

Characteristics	N=110 n	%
Sex		
- male	48	44
- female	62	56
Mean age (years)	45.4 ± 11 [28-67]	
Main activity		
- surgical	59	54
- reproductive medicine	21	19
- medical gynecology	22	20
- obstetrics	8	7
Practice		
- public hospital	61	55
- private clinic	49	45
Average number of years of practice (years)	15 ± 10.5 [1-36]	

Table 2: Situations in which our practitioners offered fertility preservation

Situations	N=	%
Bilateral endometrioma	65/84	77
Unilateral endometrioma	24/73	33
Recurrent endometrioma	70/73	96
Isolated deep endometriosis with decreased Anti-Mullerian Hormone (AMH)	68/78	87

Table 3: Studies on variation of Anti-Mullerian Hormone (AMH) rate post-operatively

	AMH rate (ng/mL)					
	Pre-operative	1 week	1 month	3 months	6 months	12 months
Lee et al. (20) Unilateral cystectomy	4.69	2.77	2.77	3.29		
Alborzi et al. (21) Unilateral and bilateral cystectomy	3.86	1.66	2.06			
Chang et al. (22) Unilateral and bilateral cystectomy	2.23	0.67	1.14	1.5		
Goodman et al. (23) No precision	1.77		1.12		1.41	
Vignani et al. (24) Unilateral and bilateral cystectomy	3.98		1.67	2.01	2.43	4.01
Sugita et al. (25) Unilateral and bilateral cystectomy	3.56		1.90			2.10