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Relationship between patient age and disease features in a prospective cohort of 1,560 women affected by endometriosis

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Short title: Endometriosis features and patient age.

Prècis

Endometriosis surgery is most frequent between the ages of 26 and 35 years, while the severity of lesions increases from adolescence until the adult period.

Abstract

Objective: To assess the relationship between age, location of disease and surgical procedures performed in patients undergoing surgical management of endometriosis.

Design: Retrospective study using data prospectively recorded in the CIRENDO database.

Setting: University tertiary referral center.

Patients: All patients who underwent surgical management of symptomatic endometriosis between April 2009 and April 2014.

Methods: Women included in this study underwent surgical management of endometriosis between April 2009 and April 2014. Patients were allocated to 6 groups according to their age at time of surgery: ≤ 20, 21-25, 26-30, 31-35, 36-40 and > 40 years. Patient characteristics, prior history, location of endometriotic lesions, stage of disease, intraoperative findings and surgical procedures were retrieved from a prospectively recorded database.

Measurements and Main Results: Patient characteristics, symptoms and location of endometriosis, and type of surgery performed were compared between groups. In total, 1,560 procedures were performed. Of these, more than one half were carried out in women between the age of 26-35 years and the majority were performed in women between 26-30 years. Only 2% of procedures were performed in women under the age of 20 years. The mean stage of the disease at time of surgical diagnosis was stage 2 before 20 years, stage 3 from 21 to 25 years,

and stage 4 over 26 years. The rate of diagnosis of deep colorectal nodules increased progressively from 20 to 26 years, and remained stable thereafter.

Conclusions: Our data confirm that endometriosis is a disease which probably progresses from adolescence until the adult period, when symptoms (pain or infertility) become debilitating and require surgery. Our data suggest that policies relating to the prevention and early diagnosis of endometriosis should focus on women under the age of 25 years.

Key words: age; endometriosis; progression; stage; surgery.

Introduction

Endometriosis is a common gynaecological disease associated with pelvic pain and infertility. The symptoms of endometriosis may have significant negative impact on patients' daily life [1-3]. The effective management of endometriosis should take into account the likelihood of disease progression, especially in younger women who have yet to achieve pregnancy. A recent study [4] reviewed laparoscopic findings in a cohort of 500 adult women who underwent surgery and unexpectedly found no correlation between stage of endometriosis and patient age. The authors concluded that revised American Society for Reproductive Medicine (rASRM) classification stage I or II endometriosis is ''equally likely to be present in women of all ages.'' They also concluded that stage III and IV disease is ''not age dependent.'' Unfortunately, this study did not include a significant number of adolescents with endometriosis.

Information on the relationship between type and severity of endometriotic lesions and patient age is, however, useful and may contribute to what is already known and debated regarding the risk of progression of the disease when left untreated over time. An observation that the rate and the severity of lesions diagnosed and treated during surgery progressively increases with patient age would suggest that growth of lesions over time is likely.

In an attempt to improve knowledge on this topic, we studied the relationship between patient age and the type, stage and location of endometriotic lesions, and the surgical procedures used to treat them, in a large prospective database.

Patients and Methods

Women included in this study underwent management of endometriosis between April 2009 and April 2014 in the Department of Gynecology of Rouen University Hospital, France. They were prospectively enrolled in the CIRENDO database (the North-West Inter-Regional Female Cohort for Patients with Endometriosis), a prospective cohort funded by the G4 Group (the University Hospitals of Rouen, Lille, Amiens, and Caen, France) and coordinated by the corresponding author of the present study (H.R.). Patient enrolment in the database commenced in June 2009 and is ongoing. To qualify for inclusion in the database, patients must undergo surgery for endometriosis, with confirmation of endometriosis via histological examination of specimens, and must complete several questionnaires. Patients who declined to fill in the questionnaires were excluded from the cohort. With the exception of Rouen University Hospital where patient enrolment has been consistent over the past 10 years, an additional 10 facilities [university hospitals, general hospitals, private clinics] have intermittently included patients in the database. As Rouen University Hospital is a center specializing in the surgical management of deeply infiltrating endometriosis, the rate of patients with deep endometriosis in the database may be overrepresented when compared to the general population. However, their management follows the guidelines and standards of practice available at the time of the surgery. Information was obtained from surgical and histological records and from patient questionnaires completed prior to surgery. Data recording, patient contact, consent and follow-up were carried out by a dedicated clinical research nurse. Postoperative follow-up was based on data from the aforementioned

questionnaires completed at 1, 3, and 5 years after surgery. Prospective data recording and analysis were approved by the French authorities (Commission Nationale de l'Informatique et des Libertés: the French data protection commission; and Comité Consultatif pour le Traitement de l'Information en matière de Recherche dans le domaine de la Santé: the advisory committee on information technology in health care research). Data recording in the database was carried out using ACCESS software.

This research was approved by the local Institutional Review Board (project number E2018-71, date of approval 19/11/2018).

The following data were retrieved from the CIRENDO database: patient characteristics, historical factors, location of endometriotic lesions, rASRM disease stage, intraoperative findings and surgical procedures performed. The frequency of these was compared between the 6 groups of patients.

Statistical analysis was performed using Stata 11.0 software (StataCorpLP). The sample of patients was divided into 6 groups according to patient age: patients ≤ 20 years of age (group A), between 21 and 25 years of age (group B), between 26 and 30 years of age (group C), between 31 and 35 years of age (group D), between 36 and 40 years (group E) and > 41 years (group F). Univariate analysis was used to compare patient characteristics, clinical history, location of lesions, intraoperative findings, and procedures carried out. Fisher's exact test was used to compare qualitative variables, and the ANOVA test and Kruskall-Wallis test were used to compare continuous variables. $P<0.05$ was considered to be statistically significant.

Results

Among the 1560 women included in the study, 32 patients (2%) were allocated to group A, 225 (14.4%) to group B, 456 (29.2%) to group C, 380 (24.4%) to group D, 259 (16.6%) to group E, and 208 (13.3%) to group F.

Deep and superficial endometriotic lesions were removed by excision. A majority of ovarian endometriomas were managed by plasma energy ablation [5]. Bowel lesions were removed by shaving, disc excision, or segmental resection. Urinary tract lesions were managed by resection of the bladder, advanced ureterolysis requiring JJ stents, ureteral resection followed by end-to-end anastomosis, or ureterocystostomy. Surgical procedures were routinely fully recorded.

Patient characteristics, medical history, surgical history and reasons for previous surgeries are presented in Table 1. More than one half of previous surgeries were carried out in women in groups C and D, while the highest rate of prior surgery was recorded in group C. There was a progressive decrease in the percentage of women greater than 30 years of age in our cohort, however more than 30% of them had undergone previous surgery for endometriosis. At least one half of women aged between 26 and 40 years had a history of infertility, however more than two thirds of women over 36 years of age had achieved a pregnancy, among whom a large majority had delivered.

Symptoms, including dysmenorrhea, dyspareunia and pelvic pain are presented in Table 2. Frequency and intensity of various types of pain were comparable between the groups, as were rates of gastro-intestinal complaints related to menses.

Intraoperative findings are presented in Table 3, showing that the rASRM stage of endometriosis progressively increased from group A to group C, and thereafter there was no significant change. The mean stage of the disease was 2 in group A, 3 in group B, and 4 in the other groups. The total operative time increased progressively following the same trend, as did the rate of patients managed for bowel endometriosis, with the highest rate between 26

and 30 years. Specifically, operative time (in minutes) was 72.6 ± 43.4 (CI 116-29.2) in Group A, 124.1 ± 96.1 (CI 220.2-28) in group B, 148 ± 105.5 (CI 253.5-42.5) in the group C, 148.9 ± 104 (CI 252.9-44.9) in group D, 132 ± 84.5 (CI 216.5-47.5) in the group E and 131.7 ± 70.2 (CI 201.9- 61.5) in group F (p <0 .001).

Hysterectomy for adenomyosis was performed in patients with no further desire to conceive; these patients represented one quarter of patients in group E, and two thirds of patients in group F.

The main distribution and location of endometriotic lesions is presented in Table 4. Between groups, there was no statistically significant difference in rate of diagnosis and treatment of superficial endometriosis. The rate of ovarian endometriosis progressively rose from 40% of patients in group A to 89.5% in group E and 97.1% in group F. The rate of diagnosis of deeply infiltrating colorectal nodules was very low before 20 years of age, then increased progressively from 20 to 26 years, then remained stable thereafter. There was an earlier trend for bladder nodules or deep posterior endometriotic nodules with or without gastro-intestinal tract involvement, which began with group B. The rASRM score progressively increased with patient age: 16.5 ± 22.7 (CI 39.2-6.2) in group A, 33.6 ± 35.8 (CI 69.4-2.2) in group B, 44.9 ± 40.1 (CI 85-4.8) in group C, 47.7 ± 43.9 (CI 91.6-3.8) in group D, 49.5 ± 42.4 (CI 91.9-7.1) in group E, 50.8 ± 42.1 (CI 92.9-8.7) in group F with a P<0 .001.

Discussion

Our study demonstrates that the severity and stage of endometriosis increases from adolescence throughout the reproductive years, which strongly suggests progression of the disease itself during this time. Our data show that deep infiltrating endometriotic lesions are rarely found in symptomatic adolescents, whilst their highest frequency is observed after the

age of 26 years. The severity and stage of endometriosis appears to increase from adolescence until the fourth decade. These data suggest that endometriosis is a disease which probably progresses from adolescence until the adult period, when symptoms (pain or/and infertility) may finally become debilitating and require surgery.

Our study has several limitations. Firstly, our cohort included women with a high prevalence of deep infiltrating endometriosis and endometriosis affecting the bowel who underwent surgery. Multiple factors may have influenced their referral to our centre, including the views of the referring gynaecologist, as well as the acceptance of surgery by the patients themselves. Our cohort did not include women managed with medical treatment exclusively, as histological confirmation of endometriosis was not available. Thus, our observations cannot automatically be extrapolated to all women with endometriosis, but only to those with symptomatic disease, who ultimately require surgery.

The second limitation is related to the interpretation of results. We reported on a cross sectional cohort, where several age groups were compared at a specific point in time. Our study does not allow us to state with certainty that the number and the severity of endometriotic lesions increase with age, however the observed increase of OR (95%CI) related to deep endometriotic lesions and advanced surgeries as patient age increased suggests that this hypothesis warrants documentation. The increase in the number and severity of endometriotic lesions is relevant from adolescence until the age of 30 years. For this reason we suggest that disease progression is likely at least until the age of 30 years, and there remains a possibility of progression beyond this threshold.

The third limitation of our study is related to the unbalanced number of patients enrolled in each group. Although the number of adolescents is small when compared to that of the whole sample, the statistically significant differences revealed in our analysis demonstrate a true difference between adolescents and older patients.

Our study has two major strengths: a large sample size and careful prospective data recording in a specialized database. Our large sample size allows us to identify several trends regarding the rate of various pre-existing patient factors, disease locations and surgical procedures used in our patients. Prospective recording of data within a specific database managed by a dedicated clinical research nurse allows for accurate analysis of data, with a low risk of error.

The pathogenesis of endometriosis is not yet fully understood [6-9]. Retrograde menstruation through the fallopian tubes is as yet only a theory, mostly based on indirect observations such as the common locations of lesions, and the correlation between the frequency of the disease and various factors that could increase retrograde flow. Recent research supports epigenetic theory, as well as the role of inflammation in the overproduction of a wide range of inflammatory mediators, that is, prostaglandins, metalloproteinases, cytokines, and chemokines, with direct impact on the development and progression of endometriosis [10]. Reactive oxygen species and free radicals favor the growth and adhesion of endometrial cells in the peritoneal cavity and consequently disease onset, its related symptoms, pain, and infertility. The accumulation of the effects of these phenomena is time-dependent, and ultimately gives birth to macroscopic lesions which may be revealed by imaging techniques or intraoperatively. With regard to the progression of deep endometriotic nodules, neither the mechanism of the development of deep endometriotic lesions is known, nor the time at which they arise. However, the growth of deep infiltrating endometriosis has been demonstrated in female baboons, in which nodules were induced and then followed up at 6 and 12 months, with specific analyses of gland morphology, collective cell migration and nerve fiber density [11]. The growth of deep rectosigmoid endometriosis nodules has recently been observed in women not receiving hormonal suppression who were followed up by successive MRI examinations [12]

Although peritoneal superficial lesions and ovarian endometriomas represent the majority of endometriotic implants within the pelvis, deep infiltrating endometriosis and extra-pelvic endometriosis are the most challenging conditions faced, and their frequency appears to increase with patient age. Despite the efficacy of medical therapy in numerous cases, surgery is often required to reduce symptoms. Hence, in a large number of patients a complete surgical eradication of disease, with nerve-sparing and vascular sparing approaches, is needed to restore normal pelvic anatomy and pelvic organ function. In our sample, the complexity of surgical procedures progressively increased from adolescence until 30 years of age, which suggests that the severity of the disease could follow the same trend. With regard to the choice of surgical procedure, when the bowel is involved, it is our policy to propose more aggressive surgery (segmental resection or disc excision) in younger women inherently at greater risk of recurrence over time, and more conservative procedures (shaving) in older women who have completed their families, where continuous medical treatment until menopause may allow for a less radical excision [13].

The most common clinical signs of endometriosis are menstrual irregularity, chronic pelvic pain, dysmenorrhea, dyspareunia and infertility. Both the frequency and intensity of these symptoms paradoxically do not correlate with disease stage or patient age. Symptoms of endometriosis often affect psychological and social functioning of patients [7]. Thus, endometriosis is considered as a disabling condition which may significantly compromise social relationships, sexual function and mental health. For these reasons, surgical management of endometriosis may be required if medical therapy is not effective in the management of pain or when assisted reproductive technology does not lead to conception.

A major observation of our study is that surgery for endometriosis is mainly recommended in women over 25 years of age, for a number of reasons. First, endometriosis may be a progressive disease, the symptoms of which progressively worsen over many years,

until surgery can no longer be delayed. It should be emphasized that the frequency and intensity of pain symptoms were similar between the six different groups of patients in our study, suggesting that in each group, we based our decision to perform surgery on similar criteria. However, these criteria were more frequently met in women over the age of 25 years, and beyond this there was no increase in symptom frequency until menopause. Furthermore, despite similar symptoms reported by each group, the stage of endometriosis progressively increased from women under the age of 20 years to those between 26 and 30 years of age, suggesting that the disease itself evolves during this period of time. The lack of association between intensity of symptoms and stage of endometriosis, as well as between gastro-intestinal complaints and infiltration of the digestive tract are in keeping with what has been previously reported in the literature [14,15].

Second, there is a recognized delay in diagnosis of endometriosis of many years from first presentation. This delay is usually estimated from the onset of initial symptoms until diagnosis. However, the first symptom reported is frequently primary dysmenorrhea during adolescence, and there is a likelihood that the disease may progress during the delay to diagnosis. Although rare, deep infiltrating endometriosis has been reported in adolescents. Recent reports suggest that adolescent endometriosis may be a progressive condition, at least in a significant proportion of cases, while deep endometriosis has its roots in adolescence [16].

Third, surgery may be prompted not only by pain but also by infertility. As the mean age of primipara in France is 30 years of age, it is logical that women aged 26-30 years are more likely to attempt to conceive, with a consecutive increase in the number of surgeries performed for infertility.

There is a progressive decrease in the proportion of patients over 30 years undergoing management of endometriosis in our department. The decrease in number of

surgeries for deep endometriosis in the group of women aged > 30 years may be explained by the use of hormonal treatment in those who no longer desire to conceive. However, we also observed an increase in the rate of previous surgeries for endometriosis in patients over 30 years of age, which suggests that in up to one third of these women the diagnosis of endometriosis and the first surgical management were performed several years prior to referral to our department. These observations suggest that the diagnosis of endometriosis and the first surgery for endometriosis mainly occur between the ages of 26 and 30 years.

The rate of deep colorectal nodules was extremely low below the age of 20 years, and increased from 20 to 26 years, then remained stable thereafter. In our series, both the highest rate and the highest number of procedures on rectosigmoid endometriosis were recorded in women aged between 26 and 30 years. This trend may support the fact that deep endometriotic nodules evolve until at least the age of 30 years. This may be important especially in women with a confirmed diagnosis of endometriosis, who benefit from medical treatment or who conceive at least once. Recent data revealed that natural progression of deep endometriotic nodules of the rectosigmoid is possible in women with normal ovarian function, while continuous medical treatment might avoid this progression [12].

This debate concerning the progressive potential of endometriosis is highly contentious. In a long prospective study of 643 consecutive laparoscopies, Koninckx et al. [17] evaluated area, depth, and volume of endometriotic lesions. The authors observed that incidence, area, and volume of subtle lesions decreased with age. For typical lesions, however, these parameters increased with age. Recently, the same group proposed a simple classification, which separately scores the severity of superficial, cystic, deep, and other lesions [18]. If implemented, such a scoring system could yield quantitative data that could be used to predict the risk of progression for each type of lesion, thus potentially resolving many of the uncertainties that hamper more effective management of endometriosis.

Notwithstanding the paucity of available evidence, it is not unreasonable to consider the time of onset of endometriosis in a patient's life cycle as an important determinant of the risk of progression [19].

Another study showed that early onset endometriosis is distinct from adult endometriosis, and also more progressive [20]. This hypothesis is based on both biological plausibility and on clinical evidence. As "nobody is born with stage 4 endometriosis" [21] and cases of deep endometriosis in adolescents are incidental, it can be presumed that endometriotic lesions could begin to grow from menarche, until the intensity of symptoms prompts diagnosis.

Some authors dispute the hypothesis of the potential of endometriosis to progress. Canis et al. [22] suggested that endometriosis may not be a chronic disease on the basis of three hypotheses: i) the natural history of endometriotic lesions may depend on the tissue in which they have developed. Local evolution may be similar to the history of metastasis: the mechanisms involved are organ-specific and result from a reciprocal reprogramming of tumor cells and of the surrounding tissue structure; ii) once the trauma has been stopped and the injured tissue repaired, the severity does not significantly increase, as it is unusual to observe a significant growth of deep infiltrating nodules of the posterior cul-de-sac after initial diagnosis; iii) disease recurrence is rare, unless new trauma induces further lesions. In most cases, other than the consequences of inappropriate surgery, the phenotype does not get much worse after the initial surgical diagnosis. Clinical recurrences may be explained more by inappropriate treatments than by unexplained or mysterious activity of the disease itself. However, these considerations do not negate our findings and the probability of growth of lesions from adolescence until the adult period.

Conclusions

Our data confirm that endometriosis is a debilitating disease, which probably progresses at least until the age of 30 years. Diagnosis and surgical management usually occur between 26 and 30 years of age. Therefore, policies relating to the early diagnosis or prevention of endometriosis should focus on women under the age of 25 years. Our findings also raise the question of the benefit of earlier surgical management of deep endometriotic nodules, prior to the involvement of the gastro-intestinal or urinary tracts [23].

Authors' role: Horace Roman and Emanuela Stochino Loi performed analysis and wrote the first draft of the report. Jenny-Claude Millochau checked data recording. Horace Roman performed surgical procedures. All authors have revised the manuscript. All authors have contributed to the writing of the final manuscript and have approved it to be published.

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Details of ethics approval: The research had been approved by the Institutional Review Board (project number E2018-71, date of approval 19/11/2018).

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Tables and figures:

Table 1: Patients characteristics and antecedents.

Table 2: Main baseline painful symptoms

Table 3: Intraoperative findings and main surgical procedures.

Table 4: Endometriosis lesions revealed during the surgery.

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Table1. Patients' characteristics and antecedents.

	Total	<20 ys		21-25 ys		26-30 ys		31-35 ys		36-40 ys		>40 ys	
	N=1560 (100%)	N= 32 (2.02 %)	OR IC95 %	N=225 (14.4 %)	Ref	N=456 (29.2 %)	OR IC95 %	N=380 (24.4 %)	OR IC95 %	N=259 (16.6 %)	OR IC95 %	N=208 (13.3 %)	OR IC95 %
Antecedents of gynecological surgery	726 (46.7)	4 (12.5)	0.4 (0.1-1.2)	58 (25.8)	1	181 (40)	1.9 (1.3-2.7)	197 (52.4)	3.2 (2.2-4.5)	158 (61)	4.5 (3.1-6.6)	128 (61.5)	4.6 (3.1-6.9)
Justification for previous surgeries													
Pelvic pain	463 (29.7)	3 (9.4)	0.5 (0.16-1.9)	36 (16)	1	130 (28.5)	2.1 (1.4-3.1)	118 (31)	2.3 (1.5-3.6)	98 (37.8)	3.2 (2.1-4.9)	78 (37.5)	3.1 (2-4.9)
Infertility	129 (8.3)	0	0	4 (1.8)	1	39 (8.5)	5.1 (1.8-14.6)	34 (8.9)	5.4 (1.9-15.5)	30 (11.6)	7.2 (2.5-20.9)	22 (10.6)	6.5 (2.2-19.3)
Ovarian cysts	153 (9.8)	0	0	10 (4.4)	1	34 (7.5)	1.7 (0.8-3.6)	49 (12.9)	3.2 (1.6-6.4)	38 (14.7)	3.7 (1.8-7.6)	22 (10.6)	2.5 (1.2-5.5)
Endometriosis	401 (25.7)	3 (9.4)	0.5 (0.1-1.7)	39 (17.3)	1	93 (20.4)	1.2 (0.8-1.8)	121 (31.8)	2.2 (1.5-3.3)	80 (31)	2.1 (1.4-3.3)	65 (31.2)	2.2 (1.4-3.4)
Adhesiolysis	161 (10.3)	1 (3.1)	0.8 (0.9-6.3)	9 (4)	1	36 (7.9)	2(1-4.3)	45 (11.8)	3.2 (1.5-6.7)	39 (15)	4.2(2-9)	31 (14.9)	4.2 (1.9-9)
Cystectomy Bilateral	126 (8.08)	1 (3.13)	1.2 (0.1-10.1)	6 (2.67)	1	30 (6.58)	2.6 (1-6.3)	42 (11.05)	4.5 (1.9-10.8)	26 (10.04)	4.2 (1.7-10.5)	21 (10.10)	4.3 (1.7-10.9)
Cystectomy Unilateral	218 (13.97)	2 (6.25)	0.8 (0.2-3.5)	16 (7 .11)	1	56 (12.28)	1.8 (1-3.2)	53 (13.9)	1.9 (1.1-3.4)	47 (18.15)	2.6 (1.5-4.6)	44 (21.15)	3 (1.7-5.5)
Documented infertility	716 (46)	1 (3.1)	0.1 (0-0.7)	59 (26.3)	1	250 (54.8)	3.4 (2.8-5.7)	223 (58.7)	4 (2.8-5.7)	127 (49)	2.7 (1.8-4)	56 (27)	1 (0.7-1.6)
Pregnancy intention at the time of surgery	735 (47.1)	5 (15.6)	0.2 (0.09-0.7)	94 (41.8)	1	294 (64.5)	2.5 (1.8-3.5)	231 (60.8)	2.2 (1.5-3)	95 (36.7)	0.8 (0.5-1.2)	16 (7.7)	0.1 (0.06-0.2)
Obstetrical antecedents													
Pregnancy*	687 (44)	1 (3.1)	0.13 (0-1)	43 (9.1)	1	131 (28.7)	1.7 (1.1-2.5)	184 (48.4)	4 (2.7-5.9)	174 (67.2)	8.7 (5.7-13.2)	154 (74)	12 (7.6-19)
Miscarriage	216 (13.8)	1 (3.1)	0.5 (0.1-4.2)	13 (5.8)	1	42 (9.2)	1.6 (0.9-3.1)	52 (13.7)	2.6 (1.4-4.9)	57 (22)	4.7 (2.5-8.8)	50 (24)	5.2 (2.7-9.8)
Delivery	575 (36.8)	0	0	21 (9.3)	1	81 (17.7)	2.1 (1. 3-3.6)	158 (41.5)	6.3 (3.8-10.4)	162 (62.5)	12.8 (7.6-21.6)	153 (73.5)	20.2 (11.7-34.7)
Ectopic pregnancy	55 (3.5)	0	0	7 (3.1)	1	12 (2.6)	0.8 (0.3-2.2)	16 (4.2)	1.4 (0.5-3.4)	12 (4.6)	1.5 (0.6-3.9)	8 (3.8)	1.2 (0.4-3.5)
Late pregnancy interruption	25 (1.6)	0	0	1 (0.4)	1	7 (1.5)	3.5 (0.4-28.5)	4 (1)	2.4 (0.3-21.4)	4 (1.5)	3.5 (0.4-31.7)	9 (4.3)	10.1 (1.3-80.7)
Voluntary pregnancy interruption	133 (8.5)	0	0	11 (4.9)	1	37 (8.1)	1.7 (0.8-3.4)	30 (7.9)	1.7 (0.8-3.4)	33 (12.7)	2.8 (1.4-5.7)	22 (10.6)	2.3 (1-4.9)

*Women get pregnant at least once

Table 2. Main baseline painful symptoms

	Total	**<20 years**		**21-25 years**		**26-30 years**		**31-35 years**		**36-40 years**		**>40 years**	
	N=1560 (100 %)	**N= 32 (2.02 %)**	OR IC 95%	**N=225 (14.4 %)**	OR IC 95%	**N=456 (29.2 %)**	OR IC 95%	**N=380 (24.4 %)**	OR IC 95%	**N=259 (16.6 %)**	OR IC 95%	**N=208 (13.3 %)**	OR IC 95%
Symtoms before surgery													
Dysmenorrhea	1471 (94.3)	30 (93.7)	0.9 (0.2-4.3)	212 (94.2)	1	438 (96)	1.5 (0.7-3.1)	358 (94.2)	1 (0.5-2)	242 (93.4)	0.9 (0.4-1.8)	191 (91.8)	0.7 (0.3-1.4)
Cyclic symptoms associated with dysmenorrhea													
Defecation pain	813 (52.1)	10 (31.2)	0.4 (0.2-0.8)	124 (55.1)	1	252 (55.3)	1 (0.7-1.4)	191 (50.3)	0.8 (0.6-1.1)	137 (52.9)	0.9(0.6-1.3)	99 (47.6)	0.7 (0.5-1)
Constipation	602 (38.6)	9 (28.1)	0.7 (0.3-1.6)	79 (35.1)	1	169 (37)	1 (0.8-1.5)	166 (43.7)	1.4 (1-2)	98 (37.8)	1.1 (0.8-1.6)	81 (38.9)	1.2 (0.8-1.7)
Diarrhea	613 (39.3)	8 (25)	0.5 (0.2-1.3)	85 (37.8)	1	190 (41.7)	1.2 (0.8-1.6)	146 (38.4)	1 (0.7-1.4)	117 (45.2)	1.3 (0.9-1.9)	67 (32.2)	0.8 (0.5-1.2)
Bloating	787 (50.4)	13 (40.6)	0.9 (0.4-1.9)	96 (42.7)	1	224 (49.1)	1.3 (0.9-1.8)	202 (53.2)	1.5 (1-2)	145 (56)	1.7 (1.2-2.4)	107 (51.4)	1.4 (1-2)
Urinary pain	407 (26)	7 (21.9)	0.6 (0.3-1.6)	68 (30.2)	1	116 (25.4)	0.8 (0.5-1.1)	99 (26)	0.8 (0.6-1.2)	70 (27)	0.8 (0.6-1.3)	47 (22.6)	0.7 (0.4-1)
Having had sexual intercourse during the last 12 months	1466 (94)	25 (78.1)	0.2 (0.06-0.5)	214 (95.1)	1	440 (96.5)	1.4 (0.6-3.1)	361 (95)	1 (0.4-2)	244 (94.2)	0.8 (0.4-1.8)	182 (87.5)	0.3 (0.2-0.7)
Deep dyspareunia (N=1466)	1125 (76.7)	19 (76)	0.3 (0.1-0.6)	189 (88.3)	1	333 (75.6)	0.5 (0.3-0.8)	272 (75.3)	0.5 (0.3-0.7)	186 (76.2)	0.5 (0.3-0.7)	126 (69.2)	0.3 (0.2-0.4)
Chronic Pelvic pain	1133 (72.6)	23 (71.9)	1 (0.4-2.3)	161 (71.6)	1	320 (70.2)	0.9 (0.6-1.3)	282 (74.2)	1.1 (0.8-1.6)	196 (75.7)	1.2 (0.8-1.8)	151 (72.6)	1 (0.7-1.6)

Table 3. Intraoperative findings and main surgical procedures.

	Total	**<20 ys**		**21-25 ys**		**26-30 ys**		**31-35 ys**		**36-40 ys**		**>40 ys**	
Intraoperative findings	**N=1560 (100 %)**	**N= 32 (2.02 %)**	**OR IC95%**	**N=225 (14.4 %)**	**Ref**	**N=456 (29.2 %)**	**OR IC95%**	**N=380 (24.4 %)**	**OR IC95%**	**N=259** (16.60 %)	**OR IC95%**	**N=208** (13.30 %)	**OR IC95 %**
Operative route													
Laparoscopy	1439 (92.2)	32 (100)	0	214 (95.1)	1	426 (93.4)	0.7 (0.6-1.5)	344 (90.5)	0.5 (0.2-0.9)	244 (94.2)	0.8 (0.4-1.8)	179 (86.1)	0.3 (0.1-0.6)
Open surgery	31 (1.9)	0	0	4 (1.8)	1	6 (1.3)	0.7 (0.2-2.6)	9 (2.4)	1.3 (0.4-4.4)	2 (0.8)	0.4 (0.18-2.4)	10 (4.8)	2.8 (0.9-9)
Robotic assistance	39 (2.5)	0	0	4 (1.8)	1	7 (1.5)	0.9(0.2-2.9)	14 (3.7)	2.1 (0.7-6.5)	3 (1.2)	0.6 (0.1-2.9)	11 (5.3)	3.1 (1-9.8)
Laparoscopy followed by open route	47 (3)	0	0	3 (1.3)	1	16 (3.5)	2.7 (0.8-9.3)	13 (3.4)	2.6 (0.7-9.3)	8 (3)	2.3 (0.6-9)	7 (3.4)	2.6 (0.6-10.1)
Douglas pouch complete obliteration	860 (55.1)	8 (25)	0.5 (02-1.1)	94 (41.8)	1	258 (56.6)	1.8 (1.3-2.5)	218 (57.4)	1.9 (1.3-2.6)	155 (59.8)	2.1 (1.4-3)	127 (61)	2.2 (1.4-3.2)
Hysterectomy	216 (13.8)	0	0	2 (0.9)	1	2 (0.4)	0.5 (0.1-3.5)	12 (3.2)	3.6 (0.8-16.3)	64 (24.7)	36.5 (8.8-151.5)	136 (65.4)	210.6 (50.8-872)
Bowel surgery	625 (40)	3 (9.4)	0.4 (0.1-1.2)	64 (28.4)	1	210 (46)	2.1 (1.4-2.9)	166 (43.6)	2.1 (1.4-3)	102 (39.8)	1.9 (1.3-2.8)	80 (38.4)	1.7 (1.1-2.6)
Shaving	302 (19.4)	3 (9.4)	0.8 (0.2-2.8)	26 (11.6)	1	82 (17.9)	1.7 (1-2.7)	63 (16.6)	1.5 (0.9-2.5)	61 (23.5)	2.3 (1.4-3.9)	67 (32.2)	3.6 (2.2-6)
Disc excision	89 (5.7)	0	0	11 (4.9)	1	39 (8.5)	1.8 (0.9-3.6)	27 (7.1)	1.5 (07-3)	11 (4.2)	0.9 (0.4-2)	1 (0.48)	0.09 (0-0.7)
Segmental resection	234 (15)	0	0	27 (12)	1	89 (19.5)	1.8 (1.1-2.8)	76 (20)	1.8 (1.1-2.9)	30 (11.6)	1 (0.5-1.7)	12 (5.8)	0.4 (0.2-0.9)
Transitory stoma	96 (6.1)	0	0	11 (4.9)	1	44 (9.6)	2 (1-4.1)	28 (7.4)	1.5 (0.7-3.2)	10 (3.9)	0.8 (0.3-1.9)	3 (1.4)	0.3 (0.1-1)
Surgical procedures on urinary tract													
Resection of the bladder	62 (3.97)	0	0	10 (4.4)	1	25 (5.5)	1.2 (0.6-2.6)	17 (4.5)	1 (0.4-2.2)	7 (2.7)	0.6 (0.2-1.6)	3 (1.4)	0.3 (0.1-1.1)

Advanced ureterolysis requiring JJ stent	136 (8.7)	1 (3.1)	0.3 (0-2.3)	22 (9.8)	1	33 (7.2)	0.7 (0.4-1.2)	43 (11.3)	1.2 (0.7-2)	20 (7.7)	0.8(0.4-1.4)	17 (8.2)	0.8 (0.4-1.6)
Ureteral resection and uretero-cystostomy	18 (1.1)	0	0	1 (0.4)	1	6 (1.3)	3 (0.3-24.9)	6 (1.6)	3.6 (0.4-30)	3 (1.2)	2.6 (0.3-25.4)	2 (0.9)	2.2 (0.2-24.1)

Table 4. Endometriosis lesions revealed during the surgery.

	Total	**<20 years**		**21-25 years**		**26-30 years**		**31-35 years**		**36-40 years**		**>40 years**	
Endometriosis localizations	N=1,560 (100%)	N=32 (2.02 %)	OR IC95 %	N=225 (14.4 %)	OR IC95 %	N=456 (29.2 %)	OR IC95 %	N=380 (24.4 %)	OR IC95 %	N=259 (16.6 %)	OR IC95 %	N=208 (13.3%)	OR IC95 %
Superficial endometriosis	1284 (82.3)	26 (81.2)	1 (0.3-2.5)	184 (81.8)	1	381 (83.5)	1.1 (0.7-1.7)	320 (84.2)	1.2 (0.8-1.8)	214 (82.6)	1(0.7-1.7)	159 (76.4)	0.7 (0.4-1.1)
Ovarian Endometrioma	1234 (79.1)	13 (40)	0.5 (0.2-1.1)	144 (64)	1	350 (76.7)	1.4 (1-1.9)	292 (76.8)	1.3 (0.9-1.9)	232 (89.5)	1.9 (1.3-2.7)	202 (97.1)	2.2 (1.5-3.3)
Diaphramatic lesion	163 (10.4)	1 (3.1)	0.3 (0.04-2.5)	20 (8.9)	1	64 (14)	1.7 (1-2.8)	47 (12.4)	1.4 (0.8-2.5)	23 (8.9)	1 (0.5-1.9)	8 (3.8)	0.4 (0.2-0.9)
Appendix nodule	69 (4.4)	0	0	11 (4.9)	1	25 (4.9)	1.1 (0.5-2.3)	16 (4.2)	0.8 (0.4-1.9)	14 (5.4)	1.1 (0.5-2.5)	3 (1.4)	0.3 (0.08-1)
Small bowel nodule	60 (3.8)	0	0	10 (4.4)	1	14 (3)	0.7 (0.3-1.5)	23 (6)	1.4 (0.6-3)	9 (3.5)	0.8 (0.3-1.9)	4 (1.9)	0.4 (0.1-1.4)
Sigmoide nodule	305 (19.5)	2 (6.2)	0.5 (0.1-2.1)	27 (12)	1	96 (21)	1.9 (1.2-3.1)	94 (24.7)	2.4 (1.5-3.8)	52 (20)	1.8 (1.1-3)	34 (16.3)	1.4 (0.8-2.5)
Rectal nodule	555 (35.6)	2 (6.2)	0.2 (0.05-0.9)	54 (24)	1	174 (38.2)	1.9 (1.4-2.8)	144 (37.9)	1.9 (1.3-2.8)	96 (37.3)	1.9 (1.3-2.8)	85 (40.9)	2.2 (1.4-3.3)
Vaginal nodule	470 (30.2)	2 (6.2)	0.2 (0.05-0.9)	54 (24)	1	154 (37.8)	1.6 (1.1-2.3)	112 (29.5)	1.3 (0.9-1.9)	76 (29.5)	1.3 (0.9-2)	72 (34.6)	1.7 (1.1-2.5)
Bladder nodule	104 (6.7)	0	0	17 (7.6)	1	41 (8.9)	1.2 (0.7-2.2)	32 (8.4)	1.1 (0.6-2)	7 (2.7)	0.3 (0.1-0.8)	7 (3.4)	0.4 (0.2-1)
Deep nodules localizations	1045 (66.9)	10 (31.2)	0.3 (0.1-0.7)	134 (59.5)	1	317 (69.5)	1.5 (1.1-2.1)	320 (84.2)	1.5 (1-2.1)	177 (68.3)	1.5 (1-2.1)	145 (69.7)	1.5 (1-2.3)
One US ligament	355 (22.7)	5 (15.6)	0.6 (0.2-1.8)	50 (22.2)	1	102 (22.3)	1 (0.7-1.5)	89 (23.4)	1 (0.7-1.6)	63(24.3)	1.1 (0.7-1.7)	46 (22.1)	1 (0.6-1.6)
Both US ligaments	120 (7.7)	2 (6.2)	0.7 (0.2-3.2)	19 (8.4)	1	35 (7.7)	0.9 (0.5-1.6)	23 (6)	0.7 (0.4-1.3)	21 (8.1)	0.3 (0.5-1.8)	20 (9.6)	1.1 (0.6-2.2)
Rectovaginal nodule	190 (12.2)	0	0	24 (10.7)	1	52 (11.4)	1 (0.6-1.8)	47 (12.4)	1.2 (0.7-2)	32 (12.4)	1.2 (0.7-2)	35 (16.8)	1.7 (1-2.9)
Rectovaginal nodule + both US ligaments	351 (22.5)	3 (9.4)	0.6 (0.2-1.9)	35 (15.6)	1	118 (25.9)	1.9 (1.2-2.9)	96 (25.3)	1.8 (1.2-2.8)	58 (22.4)	1.6 (1-2.5)	41 (19.7)	1.3 (0.8-2.2)
Abdominal wall nodule	29 (1.9)	0	0	6 (2.7)	1	10 (2.2)	0.8 (0.3-2.3)	7 (1.8)	0.7 (0.2-2)	3 (1.2)	0.4 (0.1-1.7)	3 (1.4)	0.5 (0.1-2.2)