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Fertility outcomes after laparoscopic partial bladder resection for deep endometriosis: retrospective analysis from two expert centres and review of the literature.

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ABSTRACT

Objective: To evaluate fertility outcomes after laparoscopic partial bladder resection in women with bladder endometriosis and to review the literature.

Study design: A retrospective study conducted at two tertiary referral centres –Tenon University Hospital and Poissy University Hospital (Canadian Task Force Classification Level II-2)– from July 2006 to November 2015.

Patients with bladder endometriosis who underwent either laparoscopic partial bladder resection (PBR) alone for those without posterior endometriotic lesions (PBR group) or both laparoscopic PBR and associated posterior deep infiltrating endometriosis (DIE) resection (PBR-PDIE group) were included. Pregnancy and live birth rates according to prior infertility, and associated posterior DIE resection were analysed.

Results: Thirty-four patients were included; 15 in the PBR group and 19 in the PBR-PDIE group. The median age (range) was 31 years (25-37), Seventeen patients (50%) had prior infertility. The median follow-up after bladder resection was 60.6 months (12-116). Overall, of the 25 (73.5%) patients who wished to conceive, 17 (68%) achieved pregnancies resulting in a live birth rate of 76.4 %. Among the 17 patients with prior infertility, nine (52.9%) conceived. Overall, eight patients (53.3%) in the PBR group conceived and nine (47.3%) in the PBR-PDIE group (difference not significant).

Conclusion: The present study demonstrates that laparoscopic PBR results in a high pregnancy rate in patients with prior infertility as well as in those with associated posterior DIE suggesting that surgery could be an acceptable alternative to first-line assisted reproductive technology.

Key words: bladder endometriosis – fertility - laparoscopy – partial bladder resection- deep infiltrating endometriosis

Introduction

Endometriosis is a frequent gynaecological disorder affecting 10% of women during the reproductive period and up to 50% of infertile women [1]. Bladder endometriosis is defined as detrusor infiltration by endometriosis [2] and is thought to affect 11% of women with endometriosis [3]. Bladder endometriosis represents 85% of urinary tract endometriosis [4] and is responsible for pain during micturition, haematuria, pollakiuria and voiding dysfunction. However, its impact on fertility remains unclear [5].

No guidelines have been published to date about the management of urinary tract endometriosis in the context of infertility. While first-line surgery is often recommended for ureteral endometriosis due to the impact on kidney function, it is only proposed to women with symptomatic bladder endometriosis after failure of medical treatment [5]. However, a recent meta-analysis demonstrated that laparoscopic partial bladder resection (PBR) is associated with a significant improvement in pain [6].

In the setting of infertility associated with bladder endometriosis, there is a lack of consensus as to whether first-line Assisted Reproductive Technology (ART) or first-line surgical management is recommended [7]. Data from retrospective studies involving small patient populations with bladder endometriosis suggest that surgery is associated with a relatively high pregnancy rate [8–12]. However, these data should be analysed according to the presence of associated posterior deep infiltrating endometriosis (DIE) which is a known determinant of infertility [13]. Fertility outcomes should also be evaluated by distinguishing patients with documented prior infertility from those wishing to conceive without documented infertility.

Therefore, the aim of the present retrospective study of patients with bladder endometriosis was to evaluate the fertility outcomes after laparoscopic PBR according to prior documented infertility and the association of posterior DIE, as well as to review the literature.

Materials and Methods

Study Design

We conducted a retrospective study at two tertiary referral centres – Tenon University Hospital and Poissy University Hospital – from July 2006 to November 2015. All included patients gave their consent to participate in the study before inclusion. The study was approved by the Ethics Committee of the National College of the French Gynaecologists and Obstetricians (reference number: CEROG GYN 2016-0202).

Patients

All patients aged over 18 years diagnosed with bladder endometriosis were included. Diagnosis was based on urinary symptoms (voiding dysfunction, urgency urinary, haematuria, pollakiuria, or pelvic pain during micturition), gynaecological symptoms (dysmenorrhea, non-menstrual pelvic pain and dyspareunia) and clinical examination (palpable anterior nodules in the vesico-uterine pouch), and confirmed by transvaginal sonography and by magnetic resonance imaging (MRI) using published criteria [14,15]. All the included patients had to be affiliated to the French Healthcare system and speak and read French.

Patients with prior urological surgery for benign or malignant disease or refusing surgery were excluded.

The patients were allocated to one of two groups; the PBR group composed of patients undergoing a partial bladder resection alone and the PBR-DIE group composed of patients requiring both a partial bladder resection and resection of deep infiltrating endometriosis of the posterior pelvic compartment.

Surgery

Three gynaecological surgeons experienced in minimally invasive laparoscopic endometriosis surgery performed all the surgical procedures (ED&MB&AF). All the procedures were performed with the intention of removing all the endometriotic lesions including ovarian cystectomy, uterosacral ligament resection, hysterectomy, ureterolysis, and bowel resection when required. The endometriosis score of the American Society for Reproductive Medicine (ASRM score) was calculated for all the patients. The first step of the laparoscopy consisted in exploring the abdomen to assess all locations of endometriosis. The extent of infiltration and the distance from the bladder trigone to the endometriotic nodule were then evaluated after mobilising the bladder. The objective was to perform full-thickness bladder

resection when necessary or bladder shaving. This decision was made during the procedure according to lesion size, bladder infiltration and taking into account imaging and cystoscopy features.

A double J stent was placed when the distance between the nodule and ureteric orifice was less than 2 cm. Briefly, the bladder nodule was separated from the anterior uterine wall and laterally from the round ligament. The dissection was then extended to the posterior wall of the bladder to mobilize the nodule from the vaginal wall. The nodule was either separated from the detrusor during the shaving procedure or entirely removed for full-thickness bladder resection. A single layer of resorbable suture was used to suture the bladder using intra- or extracorporeal knots depending on the surgeon. A methylene blue test was performed in all the cases to ascertain bladder integrity. A Foley catheter was left in place for 5 to 10 days after the partial bladder resections after healing had been confirmed by cystography.

Collected Data

Patient characteristics including age, body mass index (BMI), parity, previous surgery, nodule size on imaging, details of the surgical procedure performed, and size of the histological specimen were recorded. The ASRM score was systematically calculated.

Postoperative complications were classified according to the Clavien-Dindo classification system as minor (grade I-II) or major (grade IIIA and IIIB-IV).

The gold standard for the diagnosis of bladder endometriosis was the histology.

All the women had at least 6 months of postsurgical follow-up. Information about the desire to conceive after surgery was collected during initial patient intake. Events such as divorce, attempts at ART, and outcome of pregnancies and deliveries were obtained by chart review and were updated by face-to-face or telephone interviews. Infertility was defined by the absence of pregnancy for at least 12 months (World Health Organization criteria) for women wishing to conceive. All infertile women had preoperative infertility evaluation including

ovarian function, post-coital testing, hysterosalpingography, and diagnostic hysteroscopy. The partner's sperm was also examined.

Statistical analysis

Statistical analysis was based on the Student's t test as appropriate for continuous variables, and the Chi-square test as appropriate for categorical variables. Values of $p < 0.05$ were considered to denote significant differences. All analyses were performed with R software, version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Epidemiological characteristics and imaging findings of the patient population

During the study period, 38 patients underwent partial bladder resection for endometriosis without hysterectomy in the two centres. Among them, four patients were lost to follow-up. The study population was thus composed of 34 patients.

The characteristics of the study population are summarized in Table 1. The median age (range) was 31 years (25-37), and median body mass index was 22 kg/m² (16.7-18.3). Among the 34 patients, 15 patients without posterior endometriotic lesions underwent PBR (PBR group) and 19 patients required PBR with DIE resection (PBR-PDIE group). Twenty-four (70.6%) patients were nulliparous. Seventeen patients (50%) had a history of infertility. The mean duration of infertility was 40 months (12-60). Twenty-five of the 34 (73.5%) patients wished to conceive and among them 15 (60%) had documented infertility.

Characteristics of bladder nodule on imaging

In the PBR-PDIE group, bladder endometriosis associated lesions involved the utero-sacral ligaments in 10 cases (29.4%), the torus uterinum in five cases (14.7%), the parametrium in two cases (5.8%), and the colorectum in two cases (5.9%).

Fifteen of the 34 (44%) patients underwent preoperative cystoscopy which confirmed the diagnosis of bladder endometriosis in all cases. The median size of the nodules on cystoscopy was 30 mm (20-50). Eight of the nodules were trigonal and seven were supra-trigonal.

All the patients underwent preoperative MRI. The sensitivity of MRI for the diagnosis of bladder endometriosis was 88.3%. The median size of the nodules on MRI was 30 mm (7-45).

Surgical and histological characteristics of the patient population.

Endometriosis was confirmed by surgery in all the patients.

Thirty-two patients underwent full-thickness partial bladder resection and two had bladder shaving. The bladder was sutured by simple interrupted knots in 11 patients (32%) and by continuous suture in 23 (67.6%).

The median size of the bladder nodules on surgery was 32.5 mm (20-40)

Associated procedures for posterior DIE were performed during the surgery in 19 (56%) patients and included resection of the uterosacral ligaments in ten cases (29.4%), the torus uterinum in five cases (14.7%), the parametrium in two cases (5.8%) and the colorectum in two cases (5.8%) (Table 1). Two patients required a cystectomy for endometrioma (5.8%). One patient (2.9%) required a uretero-cystostomy.

In the PBR group only, one patient (6.7%) had a cystectomy for endometrioma.

The mean ASRM score was 30.5 (6-111).

According to the Clavien-Dindo classification, one patient (2.9%) experienced a grade 1 complication (umbilical abscess), and four patients (11.7%) a grade 2 complication (two urinary infections treated by antibiotics, one incomplete healing of the bladder at cystography requiring a prolonged bladder catheterization by a Foley catheter for 50 days, and one pelvic

abscess requiring a treatment by antibiotics). No grade III, IV, or V complications occurred (Table 1).

Two patients in the PBR-PDIE group (10.5%) experienced postoperative voiding dysfunction and required self-bladder catheterization as opposed to none in the PBR group ($p=0.16$).

Fertility outcomes

Overall, the median follow-up after the partial bladder resection was 60.6 months (12-116).

The characteristics of the 25 patients (73.5%) who wished to conceive are summarized in Table 2. Among them, 17 patients (68%) conceived: 12 spontaneously (70.5%) and five after ART (29.5%). The median time to conception was 7 months (2-30). Thirteen of the 17 patients (76.5%) resulted in a live birth: six by caesarean section and seven by vaginal delivery. Three miscarriages (17.6%) and one ectopic pregnancy (5.8%) occurred during the study period (Table 2).

Seventeen of the patients (50%) had prior documented infertility. Nine (52.9%) of these patients conceived: six (66.6%) spontaneously and three after ART (33.3%). The median time to conception was 7 months (4-20). Four patients underwent a caesarean section and two delivered by the vaginal route. Among the patients with infertility, two (22.2%) experienced a miscarriage and one (11.1%) an ectopic pregnancy.

No difference in median time to conception was found between patients with and without prior documented infertility ($p=0.6$).

Comparison of patients undergoing partial bladder resection alone (PBR group) and those undergoing both partial bladder and posterior DIE resection (PBR-PDIE group).

One patient (6.7%) of the PBR group required a laparotomy conversion due to surgical difficulty in separating the bladder nodule.

Nine of the 15 patients (60%) in the PBR group and 16 of the 19 patients (84.2%) in the PBR-PDIE group wished to conceive ($p=0.13$). Four of the 15 (26%) of the PBR group and 13 of the 19 (68.4%) of the PBR-PDIE had a history of infertility ($p=0.01$).

In the PBR group, eight patients (53.3%) conceived, three after ART and five spontaneously. The median time to conception was 4 months (3-30). All eight delivered, three patients by caesarean section and five by the vaginal route.

In the PBR-PDIE group, nine patients (47.3%) conceived, seven spontaneously and two after ART. The median time to conception was 10 months (6-15). Among them, five patients (26.3%) delivered, three by caesarean section and two vaginally. Three patients experienced a miscarriage.

No difference in median time to conception was found between patients with and without infertility ($p=0.9$). No difference in the pregnancy rate was found between the groups (Table 3).

Comment

This retrospective study in two expert endometriosis centres demonstrates that laparoscopic partial bladder resection for endometriosis results in a high pregnancy rate in patients both with and without prior infertility including those with associated posterior DIE.

The overall pregnancy rate in patients wishing to conceive after partial bladder resection was 68%, and 70% of these occurred spontaneously. Moreover, no difference in pregnancy rates was observed between patients with and without prior infertility. Few studies have focused on fertility outcomes after bladder resection for endometriosis. Kovoov et al. reported six

pregnancies including one after ART in 10 infertile patients with a live birth rate of only 40% [8]. Le Tohic et al. reported seven pregnancies among 11 patients wishing to conceive including seven infertile patients (three spontaneous pregnancies and one after ART) and four without prior infertility (three spontaneous pregnancies). In a recent review on bladder endometriosis based on these two reports, Leone Roberti Maggiore et al. concluded that the benefits of surgery on fertility are modest (42–44% pregnancy rate) and postulated that only 20–25% of women may really benefit from a surgical procedure with similar pregnancy rates achieved after a single cycle of *in-vitro* fertilization [6]. However, further recent data should be taken into account (Table 4). In a series of 53 patients with partial bladder resection, Saavalainen et al. reported 18 pregnancies among the 28 patients wishing to conceive (64%), 27% of which were spontaneous and the others after ART [11]. However, these authors did not analyse the fertility outcomes according to prior infertility [11]. Moreover, 42% of the bladder resections were performed by laparotomy which can impact fertility due to the risk of postoperative adhesions explaining the high rate of pregnancies after ART [11]. Rozsnyai et al. reported six pregnancies in a series of 15 patients including nine wishing to conceive [10]. In a series of 69 patients, Soriano et al. observed 34 pregnancies (16 spontaneous and 18 ART) among 42 patients wishing to conceive (pregnancy rate of 80.9%). In contrast to our data, most of the patients became pregnant after ART [12]. Moreover, Soriano et al. reported a pregnancy rate of 70.4% (19/27), with 73.6% (14/19) after ART, among the 27 infertile patients included in their study [12]. The difference between our results and those of Soriano et al. cannot be explained by the surgical management of bladder endometriosis as the fertility outcomes were similar between patients undergoing a partial bladder resection and those who underwent bladder shaving. However, when considering the group who underwent full-thickness bladder resection as in our population, it is interesting to note that the patients in Soriano et al.'s series [12] were older, and with more prior surgery by laparotomy (23.5%) and prior infertility (69%).

Another major issue of bladder endometriosis associated with infertility is to evaluate whether posterior DIE should be removed during the same procedure. In the present study, we observed a high and similar pregnancy rate in both the PBR group and the PBR-PDIE group, suggesting that this strategy has no negative impact on fertility. Few data have been published to date to evaluate fertility after partial bladder resection leaving *in situ* posterior DIE lesions compared to patients with bladder endometriosis alone, or both anterior and posterior resection of pelvic endometriosis. Saavalainen et al., comparing patients with bladder endometriosis alone and those with associated procedures, observed similar pregnancy rates of 67% and 62%, respectively [11]. Despite a laparotomy rate of 26% among 31 patients undergoing partial bladder resection with associated procedures, these authors reported that eight of the 13 patients (61%) wishing to conceive became pregnant including 50% of spontaneous pregnancies [11]. Soriano et al. [12], reported similar results in a series of patients after partial bladder resection including 70% of patients with associated posterior DIE. Moreover, both authors reported that the fertility rate was improved after bladder resection even in patients having been unsuccessful with ART. All these data support that concomitant resection of anterior and posterior DIE does not negatively impact fertility. However, this strategy is associated with an increased risk of complications especially of voiding dysfunction [16–18]. In the present study, two patients (10.5%) of the PBR-PDIE group experienced voiding dysfunction requiring self-bladder catheterization compared to none in the PBR group. Similarly, Rozsnyai et al. reported one case of prolonged bladder atony requiring bladder catheterization lasting more than 15 months in a patient having undergone concomitant bladder and DIE resection involving the rectum. Although the European Society for Human Reproduction and Embryology (ESHRE) guidelines underline the lack of evidence supporting the positive impact of removing posterior DIE lesions in the context of fertility, our policy is to perform both anterior and posterior resection of DIE. This approach is upheld by the results of Stepniewska et al. showing that removing DIE lesions

but leaving *in situ* colorectal endometriosis is associated with a lower pregnancy rate in women with colorectal endometriosis even after ART [19].

In addition to fertility, the objective of partial bladder resection for endometriosis is to relieve the symptoms without exposing patients to the risk of severe complications. In the present study, we observed five (14.7%) minor complications (three grade 1 and two grade 2) and no grade 3-4 complications according to the Clavien-Dindo classification. This is in contrast to Chapron et al., who reported two major complications (2.7%) (one vesico-uterine fistula, and one incarceration of the fallopian tube in the bladder suture) corresponding to grade 3 complications requiring a second surgical procedure. Rozsnyai et al. reported grade 3 complications in two women (6.7%) corresponding to vesico-vaginal fistulae [10]. In accordance with our results, Saavalainen et al. reported no high grade complications in the group of patients with bladder resection alone but three grade 3 complications (9.6%) occurred in patients undergoing associated procedures (one ileal resection, one ureteroneocystotomy and one rupture of the bladder suture) [11].

Some limitations of the present study deserve to be mentioned. First, the retrospective nature of the study cannot exclude some biases. Second, the sample size was small due to the relatively low incidence of bladder endometriosis: in Leone Roberti Maggiore et al.'s review of 35 series, only 13 (37%) involved more than 10 patients. Third, despite the inclusion of 19 patients with anterior and posterior DIE, we cannot firmly conclude whether both lesions should be operated on during the same procedure. This is in full agreement with Leone Roberti Maggiore et al. who concluded that bladder endometriosis is a challenging condition due to the coexistence of different locations of endometriosis rendering it difficult to analyse the impact of bladder endometriosis *per se* on fertility. Finally, in the context of infertility, only a randomized trial comparing first intention surgery to first intention ART could resolve this challenging issue.

Despite these limitations, our study indicates that laparoscopic partial bladder resection for endometriosis is a safe and suitable option in patients wishing to conceive. Further studies are required to determine whether posterior DIE should be removed at the same time as bladder endometriosis taking into account the morbidity of posterior DIE resection especially involving the colorectum.

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Table 1: Epidemiological and surgical characteristics of the study population

Characteristics (n= 34)	Patients
Median age (years) (range)	31 (25-37)
Median body mass index (kg/m ²) (range)	22 (16.7-28.3)
Median Parity (range)	0 (0-2)
Nulliparous n (%)	24 (70.6)
History of infertility (%)	17 (50)
Duration of infertility (mean) (range)	40 (12-60)
Prior surgery for endometriosis (%)	3 (8)
Women wishing to conceive	25 (73.5)
Mean ASRM* total score (range)	30.5 (6-111)
Stage I - Minimal	12
Stage II - Mild	4
Stage III - Moderate	6
Stage IV - Severe	7
Deep infiltrating endometriosis locations at surgery N (%)	
Uterosacral ligaments	10 (29.4)
Torus uterinum	5 (14.7)
Ovarian endometrioma (uni or bilateral)	2 (5.8)
Parametrium	2 (5.8)
Colorectum	2 (5.9)
Ureteroneocystostomy	1 (2.9)
Median size of bladder nodule (mm) (range)	32.5 (20-40)
Complications according to Clavien-Dindo classification n (%)	
No complication	29 (85.3)
Grade I	1 (2.9)
Grade II	4 (11.7)

* ASRM = American Society of Reproductive Medicine

Table 2: Comparison of patients who conceived and those who did not conceive after laparoscopic partial bladder resection

Characteristics (n=25)	Women who conceived (n=17)	Women who did not conceive (n=8)	P value
Median age (range) (years)	30.5 (26-36)	33 (29-37)	
Median body mass index (range) (kg/m ²)	22.1 (16.7-27.1)	22 (19-24)	
Median Parity (range)	0 (0-2)	0 (0-0)	
Nulliparous	11 (64.7)	8 (100)	0.009
Prior infertility	9 (53)	6 (75)	0.6
Prior pregnancy	7 (41)	0(0)	0.004
Women who conceived	17 (100)	0 (0)	
Spontaneously	12 (70.5)	0 (0)	
After ART	5 (29.5)	0 (0)	
Women who delivered	13 (76.5)	0 (0)	
Vaginal delivery	7 (41.1)	0 (0)	
Caesarean section	6 (35.3)	0 (0)	
Prior surgery for endometriosis	2 (11.8)	0 (0)	0.16
Median Nodule size (mm)	35 (25-40)	30 (30-40)	
Surgical route			
Laparoscopy	17 (100)	8 (100)	
Conversion to open surgery	0 (0)	0 (0)	
Median ASRM* total score (range)	32.9 (6-76)	31 (6-110)	
Stage I - Minimal	5	3	
Stage II - Mild	0	2	
Stage III - Moderate	5	1	
Stage IV – Severe	4	3	
Patients with partial bladder resection alone	9 (53)	2 (25)	0.19
Patients with partial bladder resection and posterior DIE resection	8 (47)	6 (75)	0.19
Deep infiltrating endometriosis locations at surgery n (%)			
Uterosacral ligaments	8 (47)	3 (37.5)	0.67
Torus uterinum	4 (23.5)	2 (25)	0.94
Ovarian endometrioma (uni or bilateral)	1 (5.8)	1 (12.5)	0.64
Parametrium	1 (5.8)	0	0.33
Colorectum	2 (11.8)	3(37.5)	0.22

Ureteroneocystostomy	1 (5.8)	0	0.33
Complications according to Clavien-Dindo classification n (%)			
No complication	14 (82.4)	8 (100)	0.08
Grade 1	1 (5.8)	0 (0)	0.16
Grade 2	2 (11.7)	0	0.33

* ASRM = American Society of Reproductive Medicine

Table 3: Comparison of patients undergoing partial bladder resection alone and those undergoing both partial bladder resection and posterior DIE resection.

Characteristics (n=34)	PBR group (n=15)	PBR-PDIE group (n= 19)	P-value
Prior infertility	4 (26.7)	13 (68.4)	0.01
Women wishing to conceive	9 (60)	16 (84.2)	0.13
Women who conceived	8 (53.3)	9 (47.3)	0.73
After ART	2 (13.3)	2 (10.5)	0.81
Spontaneously	5 (33.3)	7 (36.8)	0.83
Women who delivered	8 (53.3)	5 (26.3)	0.12
Caesarean section	3 (20)	3 (15.8)	0.76
Vaginal delivery	5 (33.3)	2 (10.5)	0.13
Miscarriage	0 (0)	3 (15.7)	0.08
Surgical route			
Laparoscopy n (%)	15 (100)	19 (100)	
Conversion to open surgery n (%)	1 (6.6)	0 (0)	0.33

PBR group: partial bladder resection alone
PBR-PDIE group: both PBR and associated posterior deep infiltrating endometriosis (DIE) resection

Table 4: Main characteristics and findings of studies investigating fertility after partial bladder resection for endometriosis.

Authors	Patients	Number of pregnancies (%)	Number of patients with infertility (%)	Number of pregnancies in infertile patients (%)	Number of spontaneous pregnancies (%)	Number of pregnancies after ART, (%)
Le Tohic, 2009	11	7 (63.6%)	7 (63.6%)	4 (57.1%)	3 (75%)	1 (25%)
Kovoor, 2010	10	6 (60%)	10 (100%)	6 (60%)	5 (83.3%)	1 (16.7%)
Rosznay, 2011	9	6 (66.7%)	NA	NA	5 (83.3%)	1 (16.7%)
Soriano, 2016	42	35 (83.3%)	27 (64.3%)	19 (70.4%)	16 (45.7%)	18 (51.4%)
Saavalainen, 2016	28	18 (64%)	NA	NA	5 (27%)	11 (73%)
Current Study	25	17 (68%)	17 (68%)	9 (52.9%)	12 (72.5%)	5 (29.5%)

NA: Not available