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Women's fertility after laparoscopic cystectomy of endometrioma and other benign ovarian tumors – a 24-month follow-up retrospective study

Marta Kostrzewa [1], Grzegorz Stachowiak [1], Monika Żyła [1], Dorota Kolasa-Zwierzchowska [2], Artur Szpakowski [1], Marek Nowak [1], Jacek R. Wilczyński [1]

1 The Department of Gynaecology and Gynaecological Oncology Mother's Memorial Hospital Research Institute of Lodz, Lodz, Poland
2 Medical University of Lodz, Lodz, Poland

Correspondence to: Jacek R. Wilczyński
The Department of Gynaecology and Gynaecological Oncology
Mother's Memorial Hospital Research Institute of Lodz
Rzgowska 281/289 , Lodz, Poland.
tel: +48 42 271 1151; fax: +48 42 271 1150 ; e-mail: jrwil@post.pl

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Abstract

OBJECTIVES: The golden standard in treatment benign ovarian cysts is laparoscopic cystectomy, but it may also influence women's fertility. The aim of the study was to compare women's fertility after laparoscopic cystectomy of endometrioma versus other benign ovarian tumors.

MATERIALS AND METHODS: Out of the 123 patients operated because of benign ovarian tumor (OT), 66 underwent laparoscopic cystectomy of endometrioma (endometrioma group) and 57 underwent laparoscopic cystectomy of other benign ovarian tumor like: functional cyst, hemorrhagic cyst, yellow body cyst or mature teratoma (reference group). OT-related data were obtained from medical documentation (diagnostic tests, medical reproductive and surgical history, clinical status during OT surgery). Follow-up data were collected by means of a telephone interview. The survey included questions focused on women's fertility during a 24-month period following the surgical treatment of OT (conception, subsequent pregnancies, recurrence of OT).

RESULTS: A 24-month follow-up period revealed that the cumulative pregnancy rate was significantly higher in reference group (RG) as compared to endometrioma group (EG), i.e. 52.6% vs. 32.3%. Lower pregnancy risk was demonstrated in a EG group vs. other benign ovarian tumors, HR=0.57 (CI 0.33–0.99; p=0.049), log-rank test p=0.045. Benign OT returned in 19.3% vs. EG 36.3%, HR= 2.5 (CI 1.16–5.55 ; p=0.019) log-rank test: p=0.0136. The EG was divided on two subgroups: women with solitary endometrioma and women with endometrioma and coexistent peritoneal endometriosis. The study showed insignificantly lower risk of pregnancy in a group of advanced endometriosis vs. solitary endometrioma group (HR= 0.79 (CI 0.34–1.83; log-rank test p=0.57; pregnancy rate 29.3% vs. 40.0%). Statistically nonsignificant higher pregnancy rate occurred in a group of women with tumor ≤50mm in size among patients with benign ovarian tumor and solitary endometrioma vs. group of women with tumor >50mm (30% vs. 61%; p=0.09).

ORIGINAL ARTICLE

CONCLUSIONS: There is a low pregnancy rate after laparoscopic cystectomy of benign OT. Moreover, pregnancy rate after cystectomy of endometrioma is significantly lower and the percentage of reccurence of endometrioma is significantly higher. That is why, the decision about surgical treatment among childbearing women must be well-considered because of the risk of subsequent surgery in the future.

INTRODUCTION

Benign ovarian tumors are often investigated during physical gynaecological examination. In a group of those lesions most often occur: endometrioma, functional cyst, hemorrhagic cyst, yellow body cyst or mature teratoma. The golden standard in treatment benign ovarian cysts is laparoscopic cystectomy (Basta *et al.* 2012). The decision about surgical treatment of the ovarian tumor depends not only on its size and morphology, but also patient's reproductive plan. Saving reproductive abilities entails with maximum ovarian and Fallopian Tube tissue-saving surgery (Basta *et al.* 2012). It is recommended to excise the cyst being over 4cm diameter and the teratomas independently to its size. It is worth to point out that the definitive diagnosis of tumor's morphology is established on the basis of histopathological examination (Basta *et al.* 2012).

Most of the studies, as yet, focus on the influence of endometrioma cystectomy on women's fertility. According to endometrioma, it occurs in 17–44% of women with endometriosis and are most common in advanced endometriosis (Busacca & Vignali 2003; Basta *et al.* 2012; Dan & Limin 2013). It is proven that it influences women's reproductive outcomes such as fertility, decreased responsiveness to ovarian stimulation and decreased rate of fertilization and implantation (Gupta *et al.* 2006; Dan & Limin 2013).

There are a few surgical approaches of treatment endometrioma like: laparoscopic cystectomy, three stage procedure where laser vaporization is preceded by drainage of the cyst then gonadothropin-releasing hormone agonist treatment, fenestration/coagulation and laser vaporization. Of these procedures cystectomy is most widely performed and has been reported to have lower rate of recurrence of endometriomas, reoperation and increased pregnancy rate (Jadoul *et al.* 2012; Dan & Limin 2013). There are lack of studies analyzing pregnancy rate or recurrence after cystectomy of benign ovarian tumors.

However, cystectomy does involve the removal of normal ovarian tissue, thus it has the potential to result in decreased ovarian reserve (Basta *et al.* 2012; Raffi *et al.* 2012; Dan & Limin 2013). Moreover, laparoscopy triggers creation of the intra-abdominal adhesions, which may also influence women's fertility.

The aim of this study was to evaluate retrospectively the women's fertility outcomes in 24-months follow-up after laparoscopic cystectomy and to compare those outcomes in endometrioma group vs. other benign ovarian tumors.

MATERIALS AND METHODS

The study involved 184 women, aged 18–40. The patients were subjected to laparoscopic cystectomy in 2009–06.2012 in the Department of Gynecology & Oncological Gynecology of Polish Mother's Memorial Hospital Research Institute of Lodz. At the beginning, retrospective analysis of medical history and indications to surgery of 184 patients was done. The parameters which had been taken into consideration included: age, parity, general, obstetric and gynecological history, history of previous abdominal surgery, pelvic inflammatory disease or endometriosis. Intra-vaginal ultrasonography on admission and intra-operative outcomes like: size of the cyst, the presence of peritoneal endometroitic implants, usage of coagulation and surgery range were also evaluated. Women with previous adnexal surgery were excluded. Patients were divided into two groups on the basis of histopathological examination: endometrioma group (EG) vs. other cysts (reference group-RG).

The survey about women's fertility 24 months after laparoscopic cystectomy was done by telephone contact with each patient. The patients gave informed consent and answered the following questions: did you make an effort to have a baby for last two years after surgery?, did you become pregnant at this time?, did you miscarried, have ectopic pregnancy or bear a child? If yes, what was the time from surgery to last menstrual period? Additional questions: was the infertility diagnosed and how? did your partner has any infertility diagnostics?, did the recurrence of the ovarian cyst occur at this time? If yes, what was the treatment of the recurrent cyst?, when was the second surgery?, what was the histopathological diagnosis?

With eight women the contact was impossible and 53 did not make an effort to become pregnant during 24 months after surgery. Eventually, the study involved 123 women who received laparoscopic cystectomy and had been making an effort to become pregnant during 24 months after surgery. Time to pregnancy was counted in months started from date of surgery to last menstrual period.

Statistical analysis

For non-parametric values χ^2 test was used. T-student test was used to compare parametric values.

The nonpregnancy rate and cyst recurrence were compared between groups using Kaplan-Meier survival analysis. The diagrams presenting nonpregnancy rate during 24-months follow-up after surgery and survival rate without recurrence of the ovarian cyst in this time were obtained. The diagrams were compared using log-rank test and Cox's proportional hazards models to

count relative chance for pregnancy rate and cyst recurrence during evaluated period. Statistical significance level adopted was $p<0.05$. Statistical analysis was done in "Statistica" version 10 Stat Soft.

RESULTS

The study population included a total of 123 women, 66 with endometrioma and 57 women with other benign ovarian tumor.

The indication for surgery were: tumors suspected for teratoma, endometrial cyst over 30mm diameter in transvaginal ultrasound (TVU) with coexistence of pain or subfertility, other unsuspected for malignancy ovarian tumors over 40mm in diameter not disappearing during TVU control for 3–6 months (after conservative treatment) or recognized in patients admitted to the hospital because of sudden onset of pelvic/ abdominal pain and suspicion of tumor torsion.

The mean age was 28.6±4.1 and 28.5±5.6 years in endometrioma (EG) and reference group (RG), respectively ($p>0.05$). 22.7% (15/66) in EG vs. 24.6% (14/57) women in RG had been pregnant before cystectomy ($p>0.05$). Previously abdominal surgery was performed in 6 (9.0%) cases in EG group vs. 4(7.0%) in RG group ($p>0.05$). In EG group 12.1% (8/66) had endometriosis before cystectomy, while for the rest of them it was the first time when endometriosis was found. None of the women from EG group reported the history of pelvic inflammatory disease. On the contrary, in reference group one patient had suffered from endometriosis and 5.26% (3/57) had a positive history of pelvic inflammatory disease.

In both groups the majority of the tumors were unilateral (Table 1). On admission mean diameter of the tumor was also similar in both groups. Excision of the cyst with careful tumor site electrocoagulation was generally performed. In EG group 62.1% (41/66) of postoperative diagnosis was advanced ovarian endometriosis with coexistent peritoneal implants and/or adhesions (III and IV degree AFS). It is worth to point out that the presence of solitary endometrioma even without peritoneal implants, qualifies the stage of endometriosis to III degree in AFS classification. In RG group most of the tumors were teratomas and hemorrhagic cysts. (Table 1.)

Fertility analysis

Generally, the pregnancy rate among 123 woman was 42.28% (52/123). Only 32.2% (23/71) of women who have not conceived had the infertility diagnosed. The reason of infertility in submitted cases was the recurrence of the ovarian cyst in 73.9% (17/23), 1/23 immunological factor, 1/23 uterine septum and unknown (idiopathic) in 4 cases. No significant differences in the course of pregnancies between both groups was noticed (Table 2).

Pregnancy rate during 24-months follow-up after laparoscopic cystectomy was compared between EG group and RG group. Pregnancy rate in EG group was significantly lower 32.3% (22/66) than in RG group 52.6% (30/57). Kaplan-Mayer estimate for nonpregnancy rate was 0.667 for EG group vs. 0.474 for RG group. Lower pregnancy risk was demonstrated in a EG group vs. other benign ovarian tumors, HR=0.57 (CI 0.33–0.99; $p=0.049$), log-rank test $p=0.045$ (Figure 1).

Considering the high percentage of postoperative diagnosis of advanced endometriosis, the comparison of nonpregnancy rate among women with ovarian endometriosis and peritoneal implants/adhesions vs. women with solitary endometrioma was carried out. 60.0% (15/25) of women with solitary endometrioma have not became pregnant for 24 months after cystectomy vs. 70.7% (29/41) with additional peritoneal endometriosis, (pregnancy rate 40.0% vs. 29.3%). The study shows insignificantly lower risk of pregnancy in

Tab. 1. Characteristic of the Groups.

	EG Group	RG Group	*p*-value
N	66	57	>0.005
Unilateral Bilateral	60 6	56 1	>0.005
Diameter of the tumor (mm)	48.9±16.3	51.1±16.6	>0.005
Surgical technique: Excision of the cyst Adnexectomy Adhesion release Conversion to laparotomy Space site electocoagulation	 65 1 41 1 66	 56 1 1 0 57	 >0.005 >0.005 <0.00001 >0.005 >0.005
Postoperative diagnosis	Solitary endometrioma: n=25 Ovarian and peritoneal implants/adhesions: n=41 AFS III: n=52 AFS IV: n=14	Hemorrhagic cyst: n=19 Simple cyst: n=13 Mature teratoma: n=21 Mucinosus cystadenoma: n=2 Fibrothecoma: n=1 Cystoadenofibroma: n=1	

ovarian endometriosis with coexistent peritoneal endometriosis vs. solitary endometrioma group, HR=0.79 (CI 0.34–1.83; log-rank test p=0.57).

Tab. 2. Characteristic of pregnancies in both Groups.

	EG Group N=66	RG Group N=57	*p*-value
Intrauterine physiological pregnancy	20	26	p>0.05
Miscarriage	1	1	p>0.05
Ectopic pregnancy	1	3	p>0.05
Total	22	30	p=0.049

Tab. 3. Pregnancy rate dependent on tumor's size.

Diameter of the tumor	≤ 50mm	>50mm	*p*-value
Pregnancy Rate in Solitary enndometrioma Group	(5/10) 50%	(5/15) 33%	0.58
Pregnancy Rate in Reference Group	(25/39) 64%	(5/18) 27.8%	0.13
Total Pregnancy Rate	(30/49) 61%	(10/33) 30%	0.09

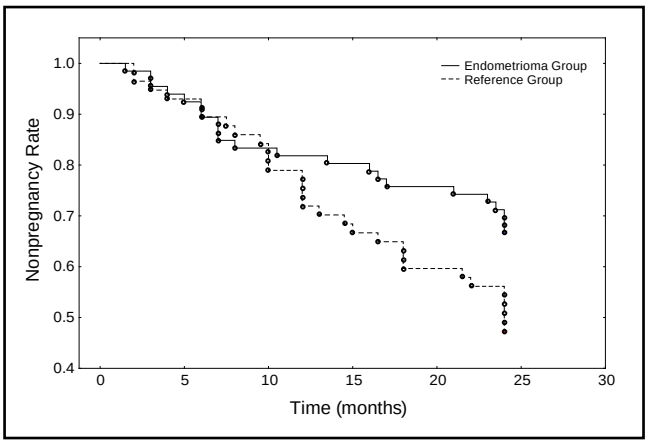

Fig. 1. Comparison of nonpregnancy rate after laparoscopic cystectomy of endometrioma and other ovarian cysts.

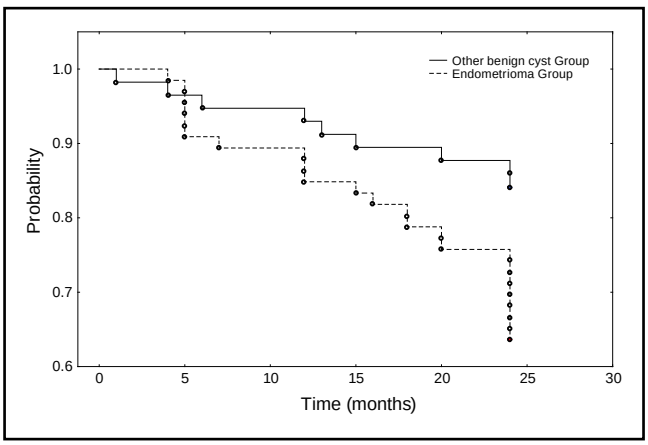

Fig. 2. Probability of survival without recurrence of the ovarian cyst.

Comparing the pregnancy rate in addition to degree of endometriosis in AFS classification we showed lower pregnancy rate in stage IV of endometriosis (3/14) 21.4% vs. (19/52) 36.5% in III stage of endometriosis (HR 0.52; 95%CI 0.15–1.76; log rank p=0.27), although it is insignificant difference.

Women's fertility was also compared in regard to the size of the excised tumor. According to the fact that women's fertility decrease with the advance of endometriosis, we excluded patients with ovarian endometriosis with coexistent peritoneal endometriosis to calculate women's fertility in regard to the size of excised tumor. (Table 3.)

The study revealed that the percentage of pregnancy after cystectomy of the tumor >50 mm in size is lower NS in comparison to the smaller-sized tumors (30% vs. 61%; p=0.09), however, the difference was not significant.

Recurrence of the cyst analysis

According to the fact that high percentage of ovarian cyst recurrence was claimed as a reason of infertility, the comparison of the risk of endometrioma recurrence vs. other benign ovarian tumor recurrence after first cystectomy was made. For 24-months follow-up the recurrence of the ovarian cyst has occurred over two times more frequently in EG group than in RG group (36.3%; 24/66) vs. (19.3%; 11/57), HR= 2.5 (CI 1.16–5.55; p=0.019) log-rank test: p=0.0136 (Figure 2).

DISCUSSION

Endometriosis occurs with a prevalence of 38% (range, 20–50%) in infertile women. (Strathy *et al.* 1982; Rawson 1991; ACOG 2000). The pregnancy rate decreases with the advance of endometriosis. There is lack of studies analyzing the influence of laparoscopic cystectomy of the ovarian cysts other than endometrioma on women's fertility.

It was proven that laparoscopic cystectomy of endometrioma measured 3–4 cm diameter and more, significantly increases the pregnancy rate in comparison to fenestration/coagulation (67% vs. 24%) (Włoczyński & Radwan 2007). This way of treatment ends successfully provided that the wall of the cyst was completely excised, which may result in five times higher chance to become pregnant. However, the surgical excision may result in ovarian tissue damage due to unintended removal of ovarian tissue adjacent to the endometrioma wall, as well as due to the use of coagulation for hemostatic purposes. Although, laparoscopic cystectomy of endometrioma seems to increase pregnancy rate in comparison to another surgical technique, our study presents that pregnancy rate in 24-months follow-up after laparoscopic cystectomy of endometrioma is significantly lower than in other benign tumor (32.3% vs. 52.6%).

Elsheikh *et al.* (2003) has counted the pregnancy rate in I and II stage of endometriosis during a 24-month

period with expectant management and it was 20.9%. Patient who have received laparoscopic surgery in I and II stage of endometriosis pregnancy rate rose to 36.7%.

Zeng *et al.* (2014) has showed that the pregnancy rate after laparoscopic surgery of endometriosis during 36 months follow up was 46.6%. The pregnancy rate differed in regard to stage of endometriosis : stage I, 53.6%; stage II, 36.0%; stage III, 51.7%, and stage IV, 41.7%, but the results were statistically nonsignificant.

Our study also didn't reveal statistical difference in pregnancy rate after laparoscopic cystectomy of endometrioma between IIIrd and IVth stage of endometriosis in AFS classification (36.5% vs. 21.4%, $p>0.05$). Moreover, our study shows insignificantly lower risk of pregnancy in ovarian endometriosis with coexistent peritoneal endometriosis vs. solitary endometrioma group (pregnancy rate 29.3% vs. 40.0%, $p>0.05$). This result confirms than ovarian endometriosis destroys strongly ovarian tissue and additional peritoneal implants/adhesions of endometriosis don't exacerbate significantly female subfertility.

Meta-analysis performed by Dan & Limin (2013) included 7 randomized controlled trials and compared outcomes such as: recurrence of endometrioma, reoperation, and pregnancy rate 12–24 months after surgery, in three groups of patients: treated by cystectomy, fenestration/coagulation or laser vaporization. The study showed that the risk of endometrioma recurrence was significantly lower (RR=0.33)and the rate of pregnancy significantly higher (RR=2.05) in patients who received cystectomy compared to those treated by either fenestration or laser vaporization. Pregnancy rate after cystectomy in 12–24 follow-up ranged in analyzed trials between 19.2–59.3% (Alborzi *et al.* 2004; Carmona *et al.* 2011), resulting in medium value of 44.8% (30/67). Recurrence of endometrioma in 12–24 months follow-up after cystectomy ranges between 0–17.3% (Alborzi *et al.* 2004; Pados *et al.* 2010), which resulted in 11.5% medium recurrence rate in meta-analysis (Dan & Limin 2013).

Yuan *et al.* (2014) revealed that endometrioma recurrence after laparoscopic cystectomy during 2-year follow up was 21.9%. Their study also presented that not only the advanced stage of endometriosis was the risk factor of recurrence (OR=1.858, $p=0.016$), but also younger age at the time of surgery (OR=0.953).

Our study presents similar results to literature as far as pregnancy rate in 24 months follow-up in endometrioma group is concerned which was 32.3% vs. 52.6% compared to other benign ovarian tumors (and further decreased to 29.3% in advanced peritoneal and ovarian endometriosis). In contrary, the percentage of endometrioma recurrence in 24 months period was considerably higher (36.3%) than in the literature (11.5–21.9%) and significantly higher than that noticed in case of other benign cysts (19.3%).

The largest part of current researches investigate the influence of endometrioma cystectomy on women's fertility in regard to IVF outcomes. However, the results of these studies are contradictory. In the review of the literature Jadoul *et al.* authors noticed that according to IVF In some studies, implantation and fertilization rates are statistically significantly lower after previous endometrioma cystectomy (Loo *et al.* 2005), but in others they are significantly higher (Esinler *et al.* 2006; Jadoul *et al.* 2012). Most of studies compared the number of retrieved and mature oocytes between operated ovaries and contralateral nonoperated ovaries and revealed increase in number of oocytes in nonoperated ovaries (Loo *et al.* 2005; Ragni *et al.* 2005; Jadoul *et al.* 2012).

Another argument supporting surgical treatment of endometrioma arises from histological analysis of endometrioma and other benign cysts. It was revealed that ovaries containing endometriotic cysts exhibited reduced follicle numbers and vascular activity compared with other types of benign cysts (Schubert *et al.* 2005; Kitajima *et al.* 2011; Jadoul *et al.* 2012).

On the other hand surgical treatment of ovarian cysts has also some drawbacks. Cystectomy causes the damage of normal ovarian tissue reducing ovarian reserve. Measuring the level AMH in circulating blood is recommended to evaluate the ovarian reserve, because AMH level is supposed to be unchangeable during menstrual period. There are researches confirming that ovarian reserve decrease after cystectomy measured by level of AMH hormone in peripheral blood (Chang *et al.* 2010; Hwu *et al.* 2011; Raffi *et al.* 2012; Somigliana *et al.* 2012; Kim JY *et al.* 2013). Some studies show that the serum AMH level at the preoperative state is lower in endometrioma than non endometrioma group. Similarly, postoperative serum level of AMH decreases much more in endometrioma compared with non endometrioma (Chang *et al.* 2010; Kim JY *et al.* 2013). That is why we can assume that ovarian reserve decrease after cystectomy and in endometriosis the decrease is more significant than in other benign cyst (Chang *et al.* 2010; Hwu *et al.* 2011; Kim *et al.* 2013). However, according to some other studies the decrease of AMH levels was not only observed in the case of cystectomy due to endometrioma but also in other benign ovarian tumors (Chang *et al.* 2010).

In addition, the decrease in the AMH level is supposed to be more severe when endometriomas are bilateral or over 5 cm in diameter (Chang *et al.* 2010; Hwu *et al.* 2011). We can explain this fact that when the cyst diameter is 5 cm there is a greater amount of tissue removed during cystectomy, so that there is a greater decrease in the AMH level.

In our research there was a trend (although insignificant) to lower pregnancy rate among patients who received cystectomy of the cyst measured over 5cm diameter (30% vs. 61% diameter ≤50 mm), which could probably reach significance in more numerous groups of patients.

Indisputably the strength of our study is that we evaluated the after-effects of laparoscopic cystectomy

not only in endometriomas but also in other benign cyst. Nowadays it is worth to consider whether surgical or expectant management of ovarian endometriomas and other benign ovarian cysts in infertile women brings higher pregnancy rate. The weekness of our study resulted from low number of patients.

CONCLUSION

Although, the pregnancy rate after cystectomy for endometrioma was significantly lower than in case of other benign cysts, the pregnancy rate after cystectomy of benign cyst was also quite low. This means that more attention should be paid to the problem of maintenance of ovarian reserve, which decreases after cystectomy without regard for histological type of the excised tumor. That is why the decision about performing cystectomy among childbearing women, should be well-considered and planned, as well as carefully performed with special regard to spare as much ovarian tissue as possible. It is exceptionally important in endomerioma cases where the recurrence rate is quite high resulting in the risk of subsequent surgery in the future.

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