Endometrial Polyps Effect on Pregnancy Outcomes in Infertile Women with Minimal/Mild Endometriosis: A Retrospective Study

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Research Article

Keywords: endometrial polyps, endometriosis, infertility, pregnancy outcome

Posted Date: January 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-145883/v1

Abstract

Background: The infertile patients with endometriosis had a higher prevalence of endometrial polyps. The effect of endometrial polyps on pregnancy outcomes in endometriosis-associated infertility patients is unclear. This study assessed the pregnancy outcomes and associated influencing factors of pregnancy after hysteroscopy combined with laparoscopy treatment in infertile patients with minimal/mild endometriosis.

Methods: We enrolled 898 infertile women who underwent both hysteroscopy and laparoscopy treatment. Based on the existence of endometrial polyps confirmed by hysteroscopy and pathologic examination, patients were divided into polyps group and non-polyps group, and their pregnancy outcomes were compared.

Results: After removal of 136 subjects who were lost to follow-up, underwent assisted reproduction techniques, or postponed plans to become pregnant. A total of 271 women were included in polyps group and 491 in non-polyps group. The pregnancy rate of polyps group was not statistically significant compared with non-polyp group (60.15% VS. 58.25%). The pregnancy rate was higher among patients with polyps ≥ 1 cm (76.06%, 54/71) than patients with polyps < 1 cm (54.50%, 109/200) or patients without polyps (58.25%, 286/491) (p = 0.006). The pregnancy rate was higher for patients with multiple polyps (67.86%, 95/140) than for patients with single polyp (51.91%, 68/131) or without polyps (p = 0.025).

Conclusions: Compared with those without endometrial polyps, single polyp, and size of polyp < 1 cm, hysteroscopic polypectomy did significantly increase fertility in infertile patients with multiple polyps or size of polyp ≥ 1cm. The size and number of polyps were independently associated with the reproductive ability of women with minimal/mild endometriosis.

Introduction

Endometriosis refers to the occurrence of endometrial glands and stromal implants growing out of the uterine cavity, which affects approximately 5–10% of general female population [1]. According to a cohort study [2], women with endometriosis had an age-adjusted 2-fold increased risk of incident infertility when compared with those women without a history of endometriosis, which is called endometriosis-associated infertility. The association between infertility and endometriosis has been widely connected to severe pelvic adhesions in moderate to severe disease that a variety of anatomical abnormalities and ovarian cysts can hinder ovum capture and transport [3, 4]. However, the impact of early-stage endometriosis on infertility remains uncertain as the effect of pelvic adhesion is not so severe. The mechanism to cause infertility in minimal/mild endometriosis may involve in the abnormal immunological environment, ovulatory dysfunction, defective implantation, and eutopic endometrium abnormalities [5, 6]. Laparoscopic surgery, which is used as the most common approach for the treatment of minimal/mild endometriosis, can improve these women's natural fertility [7, 8].

In 2003, Kim et al. had report [9] that the prevalence of endometrial polyps in the endometriosis group and in the non-endometriosis group was 46.7% and 16.5%, respectively. Endometrial polyps in endometriosis might be cofactors in female infertility, as the prevalence of endometrial polyps can reach to 47.83%-68.35% in endometriosis-associated infertility women, significantly higher than those infertile women without endometriosis [10–12]. Meta-analyses confirmed a significantly higher risk of endometrial polyps in women with endometriosis [13]. The mechanisms of endometrial polyps in endometriosis may involve in local inflammation, endocrine disorder, and hormone levels [9, 10]. As endometrial polyps are the underlying cause of infertility, removal of polyps can significantly increase pregnancy rates in these women. Hysteroscopy is the preferred technique for polypectomy for direct visualization while removing polyps and protecting adjacent endometrial integrity [14]. Our previous study revealed that the pregnancy rates were 49.52% after hysteroscopic polypectomy, 29.79% for those without polyps in the infertile women with endometriosis; furthermore, in the early stages (stages I and II) of endometriosis, the pregnant rate (63.64%) in women with endometrial polyps was higher than those without (37.14%) [15]. This suggested that endometrial polyps might be a crucial factor in infertility for women with early-stage endometriosis, hysteroscopic examination to ascertain and simultaneously remove any coexisting endometrial polyps and pelvic endometriotic foci is recommended. Nowadays, hysteroscopic polypectomy and removal of endometriotic foci could significantly improve pregnancy outcomes in women with minimal/mild endometriosis. But the contribution of endometrial polyps to infertility or pregnancy outcome has not been precisely determined. Additionally, it is unclear if the polyp size and number impact on the fecundity of infertile women with minimal/mild endometriosis. The aim of the study was to evaluate and compare the pregnancy rates after hysteroscopic polypectomy in infertile women with minimal/mind endometriosis and endometrial polyps less than 1 cm, and those equal to or greater than 1 cm or multiple endometrial polyps.

Materials And Methods

The infertile women diagnosed as the early stage of endometriosis in the Department of Reproductive Endocrinology in West China Second University Hospital of Sichuan University from Jan. 2016 to Sep. 2018 was reviewed. All participants consented to the anonymous use of their personal data. Infertility was defined as failing to conceive after at least 1 year of regular, unprotected intercourse. Diagnosis of minimal or mild endometriosis was based on laparoscopically staging as revised American Fertility Society (r-AFS) score < 16 [16]. The inclusion criteria were women with regular menstrual cycles and/or ovulation confirmed by ultrasound or luteinizing hormone(LH) kits, no hormonal treatment 3 months before surgery, and a complete fertility evaluation. The exclusion criteria included severe pelvic adhesion, lateral or bilateral tubal blockage, adenomyosis, leiomyomas, endometrial hyperplasia, decrease of ovarian reserve (DOR), ovulatory disorder (such as polycystic ovary syndrome, diabetes, thyroid diseases, or adrenal diseases), and abnormal male sperm and/or sexual dysfunction.

Women who fulfilled the inclusion criteria had their demographic and baseline characteristics data collected and reviewed, such as age, menarche age, menstrual cycle, menstruation duration, duration of infertility, history of fertility; the body weight and height of all participants were measured to calculate

their body mass index (BMI). All patients underwent laparoscopy and hysteroscopy simultaneously. In the laparoscopic procedure, pelvic or peritoneal endometriotic foci were removed by excision or electrocoagulation, and staging of endometriosis was performed according to r-AFS classification; the endometriosis fertility index (EFI) scores were obtained for each patient. Meanwhile, hysteroscopy was performed to ascertain and remove endometrial polyps using micro-scissors or an electric loop; the number and size of endometrial polyps were recorded which was obtained from further pathologic examination. After surgery, all participants attempted to conceive naturally and were followed-up to investigate their pregnancy and pregnant outcome by outpatient visit or regular phone questionnaire. The clinical pregnancy was defined as the presence of an intrauterine gestational sac with fetal cardiac activity by ultrasonography.

All were analyses were performed using the Statistical Package for Social Sciences (SPSS version 22.0, IBM, USA). The continuous variables were presented as mean ± standard deviation. Descriptive variables were transformed into categorical variables and presented as percentages. The groups were compared using t-test for normally distributed continuous data and using the Student's t-test, Mann Whitney-U test, Chi-square test, or Fisher’s exact test where appropriate. The effect of various covariates on post-operation conception was estimated using binary logistic regression analysis. Differences associated with $p < 0.05$ were defined as statistically significant.

Results

Among 898 subjects enrolled in the study, there were 338 (37.64%) diagnosed pathologically endometrial polyps, and other 560 cases with no endometrial polyps under hysteroscopy. In the polyps group, participants were divided into < 1 cm group (n = 253) and ≥ 1 cm (n = 85) according to the size of polyps, and divided into single polyp group (n = 173) and multiple polyps group (n = 165) for those having ≥ 2 polyps, respectively. 12.14% (109/898) patients (59 with polyps and 50 non-polyps) were lost to follow-up; another 27 cases (8 with polyps and 19 non-polyps) were excluded from the study as 7 having no desire to conceive and 20 taking assisted reproductive techniques after surgery. The remaining 762 women had their reproductive outcomes analyzed. The characteristics of 898 infertile women with minimal/mild endometriosis were shown in Table 1.

There were 449 natural pregnancies during follow-up, 163 in the polyps group, and 286 in non-polyps; among them, 35 spontaneous miscarriages, 8 ectopic pregnancy,11 premature labor, 389 full-term labor, and remaining 6 patient ongoing pregnancy whose gestational week over than the first trimester (Table 2). The pregnancy rate in patients whose polyps ≥ 1 cm (76.06%, 54/71) was significantly higher than those polyps < 1 cm (54.50%, 109/200) and non-polyps women (58.25%, 286/491) ($p = 0.006$); pregnant rate in women with multiple polyps (67.86%, 95/140) was significantly higher than those with single polyp (51.91%, 68/131) ($p = 0.025$).

The binary logistic regression analysis was performed to analyze covariates for pregnancy in infertile patients. The clinical pregnancy rate was the dependent variable; age, BMI, infertile duration, type of

infertility, and the existence of polyps were counted as the independent variables. In patients with polyps, the size of polyps and the number of polyps were used as the independent variables additional to previous variables. The modified Hosmer–Lemshow goodness-of-fit x^2 test statistics were 2.374 (P = 0.936) and 10.940 (P = 0.205), which suggested that the multivariable models were good fit (P > 0.05). The results revealed that age, BMI, and infertile duration significantly related to clinical pregnancy in patients with minimal/mild endometriosis (Table 3). For patients with polyp,the logistic regression analysis results showed that age, BMI, infertile duration, the size of polyps, and the number of polyps impact their pregnancy (Table 4).

Discussion

The endometrial polyps localized endothelial lesions comprise endometrial glands, stroma, blood vessels, and fibrous tissue that result from localized, hyperplastic overgrowth of the endometrium. Endometrial polyps are common in those with infertility with a prevalence as high as 32% [17]. Additionally, endometrial polyps are frequently unrecognized if they are small, which can cause unpredictable bleeding or may be asymptomatic. The mechanism of endometrial polyps on reducing women's fecundity is unknown. It is considered that endometrial polyps may alter the uterine environment as space-occupying lesions in a way that threatens sperm transport and embryo implantation; and the increased levels of glycodelin, aromatase, or inflammatory markers, and reduced levels of HOXA-10 and HOXA-11 messenger RNA adversely impact endometrial receptivity [18].

Studies [10–15] suggested that endometriosis is associated with a significantly greater risk of endometrial polyps. The precise pathogenesis of endometrial polyps in a background of endometriosis is unclear. The most widely accepted theory is that the two diseases are estrogen-dependent as both of them include the overgrowth of the endometrium; besides, eutopic endometrium inflammation may provide another perspective for the contemporary appearance of endometriosis and endometrial polyps [18, 19]. One approach to endometrial polyps can be associated with a disruption of this essential process by impeding some combination of embryo transport and subsequent implantation into the endometrium. Upon hysteroscopy, polyps appear soft and smooth and often present only a small degree of vascularization. As hysteroscopy provides both diagnostic and therapeutic capabilities, and it can be significantly more accurate than TVUS (transvaginal ultrasound) or HSG (Hysterosalpingography) at the detection of intrauterine disorders. Even if TVUS and HSG do not suggest endometrial polyps, hysteroscopy is strongly recommended for women under evaluation for infertility [9, 20]. Hysteroscopy is also the most effective way to remove endometrial polyps under direct vision, because blind dilatation and curettage may frequently leave residual tissue or miss the whole polyp. A number of studies revealed that hysteroscopy polypectomy improves success rates of intrauterine insemination (IUI) and in vitro fertilization - embryo transfer (IVF-ET) [21, 22]. In this study, we observed a spontaneous pregnancy rate above 58% among women with minimal/mild endometriosis after hysteroscopic polypectomy and removal of endometriotic foci, regardless of whether the patients had endometrial polyps. This result is consistent with our previous studies [15]. Above demonstrated that functional endometrial polyps are

likely to impair fertility. Removal of such lesions may improve subsequent reproductive performance. Therefore, removal of endometrial polyps contributes to infertility irrespective of the size or number of the polyps. Earlier study revealed that removal of polyps less than 1.5 cm in maximum diameter did not improve the result of ET [23]. Another study found pregnancy rate after hysteroscopic polypectomy increased at 61.4%, as well as the delivery at term rate was 54.2%, independent of size and number of polyps [24]; hysteroscopic removal of even small polyps is recommended to improve reproductive outcome in infertile women undergoing assisted reproductive technology [22].

Some structural abnormalities of the uterus may not have any apparent impact on these aspects of normal fertility, a circumstance that begs a number of questions. In this study, the pregnancy rate was higher in women whose polyps size ≥ 1 cm or with multiple polyps. The logistic regression analysis results showed that size and number of polyps, as well as age and infertile duration, are statistically significant risk factors for pregnancy. The effect of endometrial polyp size and number on pregnancy outcome is inconsistent resulting from different study populations and infertile etiology [22–24]. According to our understanding, this is the first study that focused on the size and number of polyps in early-stage endometriosis, showing that larger size or multiple polyps through hysteroscopic polypectomy accomplish higher pregnancies in these patients with minimal/mild endometriosis. Another study finding is the spontaneous abortion rate in the first trimester is less than 5% in women with or without polyps. It indicates that hysteroscopy is beneficial for successful live birth by improving the intra-uterine environment.

For the patients with endometriosis-associated infertility, Endometriosis Fertility Index (EFI) is considered as a simple, robust, and validated clinical tool that predicts the probability of postoperative pregnancy in infertile patients with endometriosis [25]. Our retrospective study confirmed the value of EFI scores in prediction of the fertility of endometriosis and suggested that the optimal cut-off point is 7.5 [26]. The EFI of including participants with early-stage endometriosis was over 7. Therefore, the EFI score is not an independent risk factor for pregnancy outcomes in this study population. In fact, the uterine abnormality is also one factor to predict pregnancy that is not included in the EFI. The results of logistic regression analysis in this study revealed that polyps, especially size and number of polyps should be an important factor that impacts subsequent pregnancy.

Conclusions

The present study has some limitations. It is retrospective in design, and the data necessary for polyps were collected in a single medical unit. Confounding factors included bias and lack of a standardized method to the accurate evaluated size of the polyp. A multi-center randomized controlled trial is needed to verify and extend our findings. In conclusion, despite these limitations, age, BMI, infertile duration, the size and number of polyps are independent risk factors of pregnancy outcomes in infertile patients with minimal /mild endometriosis.

List Of Abbreviations

r-AFS: Revised American Fertility Society

LH: Luteinizing hormone

DOR: Decrease of ovarian reserve

BMI: Body mass index

EFI: Endometriosis fertility index

TVUS: Transvaginal ultrasound

HSG: Hysterosalpingography

IUI: Intrauterine insemination

IVF-ET: In vitro fertilization - embryo transfer

Declarations

Statement of Ethics

The study was performed in accordance with the Declaration of Helsinki. The study design was approved by the Institutional Review Board of West China Second University Hospital, Sichuan University (approval number K1017042-1; May 30, 2018). Informed Consent was obtained by all participants to the anonymous use of their personal data.

Published statement

Not applicable.

Availability of Data

Data supporting the results of this study are available from the corresponding authors. The data cannot be made public because of privacy or ethical restrictions.

Competing interests

The authors declare that they have no competing interests.

Funding

Supported by a National Key Research and Development Project (2017 YFC1001200), the National Natural Science Foundation of China (81370693) and the Programs for Science and Technology Development of Sichuan (2018SZ0124).

Authors' contributions

W.H. designed the study; Y.X., Y.L. and X.H. collected reviews of medical history and surgical records; Y.X. was responsible for follow up; Y.X. and Y.O. were responsible for data analysis; Y.X. and H.Z. wrote the paper.

Acknowledgments

Thank for help of data analysis by Dr. Hui Chen, and language revised by Mr. Ruibo Zhang.

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Tables

TABLE 1 Demographic characteristics of 898 infertile women with minimal /mild endometriosis.

	Polyps group (n=338)	Non-polyps (n=560)
Age (yr)	29.52 ± 4.13	29.66 ± 4.00
≤35	311	516
36–39	19	33
≥40	8	11
Menarche age (yr)*	12.25 ± 0.84	11.81 ±1.10
Menstrual cycle (days)	28.78 ± 2.94	29.02 ± 2.63
Menstruation duration (days)	5.13 ± 1.15	5.25 ± 1.11
Gravidity*	0.59 ± 0.99	0.96 ± 1.27
Parity	0.10 ± 0.29	0.12 ± 0.33
Duration of infertility (yr)	2.65 ± 2.00	2.42 ± 1.67
Primary infertility (n)	215	265
Secondary infertility (n)	123	295
BMI (kg/m^2)	20.98 ± 2.68	20.82 ± 2.62

Note: Values are expressed as n or mean ± standard deviation; BMI = body mass index. *$p < 0.05$

TABLE 2 Pregnancy outcomes of 762 infertile women with minima/mild endometriosis.

	Polyps group (n=271)	Non-polyp (n = 491)
Clinical pregnancy rate	60.15%(163/271)	58.25%(286/491)
Pregnancy outcome		
Miscarriage	11	24
Ectopic pregnancy	4	4
Premature labor	7	4
Full-term labor	140	249
Ongoing pregnancy	1	5

TABLE 3 The relationship between pregnancy and related variables by logistic regression analysis in women with minimal/mild endometriosis.

Variables	B	SE	Wald	*P*	OR	95% CI of OR	
						Lower limit	Upper limit
Age (yr)*	-.676	.275	6.042	.014	.509	.297	.872
BMI (kg/m^2)*	.534	..252	4.502	.034	1.706	1.042	2.793
Duration of infertility (yr)*	-.472	.191	6.125	.013	.624	.430	.907
Type of infertility	-.069	.156	.195	.659	.934	.688	1.267
Polyps	.073	.159	.210	.647	1.076	.788	1.469
Constant	.458	.129	12.556	.000	1.582		

Note: SE = standard error; OR = odds ratio; CI = confidence interval; BMI = body mass index.

* $P < 0.05$; The modified Hosmer–Lemshow goodness-of-fit x^2 test statistics was 2.374 ($P = 0.936$).

TABLE 4 The relationship between pregnancy and related variables by logistic regression analysis in women with endometrial polyps

Variables	B	SE	Wald	*P*	OR	95% CI of OR	
						Lower limit	Upper limit
Age (yr)*	-1.121	.512	4.794	.029	.326	.119	.889
BMI (kg/m^2)*	.931	.457	4.143	.042	2.537	1.035	6.219
Duration of infertility (yr)*	-.680	.321	4.496	.034	.507	.270	.950
Type of infertility	.568	.293	3.762	.052	1.765	.994	3.133
Size of polyps *	.971	.341	8.118	.004	2.642	1.354	5.153
Number of Polyps *	.551	.268	4.230	.040	1.736	1.026	2.936
Constant	-.140	.230	.373	.542	.869		

Note: SE = standard error; OR = odds ratio; CI = confidence interval; BMI = body mass index.

* $P < 0.05$; The modified Hosmer–Lemshow goodness-of-fit x^2 test statistics was 10.940 ($P = 0.205$).