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Fertility outcome after saline sonography guided removal of intrauterine polyps in women with unexplained infertility

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polyps, clinical pregnancy rate, unexplained infertility

Abstract

Objective: To assess the effect of removal of unsuspected polyps as delineated on saline sonography on the clinical pregnancy rate in women with unexplained infertility. **Methodology:** A prospective case control study was being conducted from 1st October 2016 to 30th September 2018 at Aziz Medical Centre, Karachi. Women diagnosed with unexplained infertility and unsuspected polyps revealed on saline sonography were included as cases (Group A). They were offered removal of polyps under ultrasound guidance and general anesthesia. Saline sonography was repeated at the time to ensure complete removal (Izhar's Modification). Those with unsuspected polyps on saline sonography, but who refused the intervention, were classified as controls (Group B). Both groups were followed for one year. The primary outcome measure was women who had clinical pregnancy i.e. fetal heartbeat present on transvaginal scan during the follow up period. **Results:** During the study period, out of 92 cases, 37 (40.2%) conceived and out of 92 controls, 10 (10.9%) conceived, which proved that polypectomy increased the chances of conception four-fold (p <0.001). The mean time to conception was also significantly lower for cases than controls (9.26 ± 3.928 months *vs.* 11.33 ± 2.07 months, p <0.001). The cumulative pregnancy rate was significantly higher in the polypectomy group (log-rank test, p <0.001). The duration of infertility (p = 0.007), position of polyp (p = 0.049) and polypectomy (p <0.001) influenced pregnancy rate. **Conclusions:** Our study shows the beneficial effect of removal of polyps. Women are four times more likely to conceive spontaneously after polypectomy.

Introduction

It is estimated that infertility affects 1 in 7 heterosexual couples. The main causes of infertility are unexplained infertility (25%), ovulatory disorders (25%), tubal damage (20%), male factor causing infertility (30%), uterine or peritoneal disorders (10%). In about 40% of cases, disorders are found in both men and women. Uterine or endometrial factors, gamete or embryo defects, and pelvic conditions such as endometriosis may also play an important role[(1)].

A couple is said to suffer from unexplained infertility if the cause of infertility remains unknown after complete infertility workup[(2)]. Around 30% of couples are put in the category after the usual workup and referred for assisted reproductive technologies[(3)].

In vitro fertilization (IVF) is a novel and expensive assisted reproductive technology with a success rate of 30%[(4)]. This high failure rate of the technology renders itself as an emotionally and financially draining experience for the couple[(5)].

The role of uterine cavity in successful implantation is of paramount importance. Unsuspected subtle abnormalities affect implantation and reduce chances of conception. In a study to assess the role of hysteroscopy prior to artificial reproductive technologies (ART) in women with unexplained infertility, 31.8% had intrauterine lesions; polyps being the most common pathology[6].

The ESHRE (European Society for Human Reproduction and Embryology) and RCOG (Royal College of Obstetricians and Gynecologists) do not recommend saline infusion sonography or hysteroscopy as the initial infertility investigation. Their stance on the subject is derived from the fact that removal has not been proven worthwhile[7].

Studies showing improved clinical pregnancy rates in women with unexplained infertility after removal of unsuspected polyps are being reported. Cochrane database review concluded that hysteroscopic removal of submucous fibroids in women suffering from otherwise unexplained infertility may be beneficial[8].

Diagnosing a couple with unexplained infertility without taking a look at the uterine cavity leads to psychological and financial burden on the couple. The next step in management is IVF, which in a developing country like ours is not provided in the public sector hospitals, is expensive and has a low success rate. If uterine cavity is explored once before reaching on this diagnosis, we anticipate that unexplained infertility can be explained in a vast majority of cases.

The present study assesses the effect of removal of unsuspected polyps as delineated on saline sonography on the clinical pregnancy rate in women with unexplained infertility.

Materials and methods

Subjects

Women aged 20 to 40 years with unexplained infertility were recruited for this study from infertility clinic at Aziz Medical Centre in Karachi, Pakistan, from 1st October 2016 to 30th September 2018. Unexplained infertility was defined as 24 months of regular unprotected sexual intercourse where semen analysis was reported within normal limits, hysterosalpingogram was unremarkable and evidence of regular ovulation was present, i.e. progesterone of 30 ng/ml at mid luteal phase. Subjects were recruited initially by the researchers to undergo saline sonography in order to identify women with unsuspected polyps. Those with polyps were included in the study. Women with history of taking hormonal medications, thyroid disorder, previous hysteroscopy at any time and intermenstrual blood loss were excluded. Also, women whose polyps were removed but were not confirmed on histopathology were also excluded.

Written and informed consent was taken from all women. Those who met the inclusion criteria were referred to and underwent saline infusion sonography (SIS) on 8th to 11th day of their menstrual cycle.

Saline infusion sonography (SIS)

At the first visit, those consenting to SIS, had the procedure done in the outpatient department of the center. The technique for the procedure was as follows: A sterile Cusco's speculum was inserted into the vagina and a cervical Foley's catheter of 5–7 French was inserted through the cervical os. The bulb of the Foley's catherer was distended with 1–2 ml of saline, and then the endometrial cavity was distended by instilling normal saline through the cervical Foley's catheter. This allowed delineation of the cavity against the saline medium.

A Mindray DP-2200 scanner with a 5 to 7.5 MHz frequency endovaginal transducer was used to scan the uterine cavity. All scans were performed by a specialist with 10 years of experience. Real-time transvaginal ultrasound was used to scan the uterine cavity for any defects. The findings of the procedure were recorded on the proforma. In the case when intrauterine abnormalities were visualized on the scan, they were classified as endometrial polyps, septae and adhesions.

A polyp was suspected when an endometrial outgrowth exceeded 5 mm. The ideal method for diagnosing the endometrial polyp is a Doppler scan which reveals a straight vascular pattern in the stalk of the attachment area. Due to financial implications a Doppler scan was not used.

If the patient had polyps, she was offered another saline infusion sonography after 6 weeks and 12 weeks. It ensured that polyps had not regressed on its own. If the polyp did not regress, she was counseled for its removal. Removed polyps were sent for histopathological analysis for confirmation in all cases. If histopathology did not confirm a polyp, the case was excluded from the analysis.

Sample size estimation

To calculate an adequate sample size, we searched the literature for cumulative pregnancy rates in women with unexplained infertility. Literature reports that hysteroscopic removal of polyps before intra uterine insemination (IUI), compared with diagnostic hysteroscopy and biopsy, significantly increased the odds of clinical pregnancy (63% vs 28%, respectively)[9]. Assuming that the patients do not conceive because of a uterine factor, with a power of 80% (1-β) and a one-sided 0.05 risk of type I error (α), we needed 32 patients with polyps in each group to demonstrate a similar rise in pregnancy rate via polypectomy after visualization on saline sonography and show superiority of polyp removal in this group of patients. In

order to compensate for protocol deviation a minimum of 100 women were included in each of the groups – the cases and the controls.

Cases and controls

Women, whose polyps were removed constituted group A (CASES). Cases where polyps were not amenable to removal were not included in the final analysis. Women who did not consent to the removal functioned as group B (CONTROLS). They were followed for the study duration but not offered removal after the initial enrolment, till the completion of study. Those who requested removal later on during study period were also excluded to avoid protocol deviation.

Intervention (Izhar's modification for removal of polyp)

Informed consent was taken and after prophylactic antibiotics, the procedure was performed under general anaesthesia. A saline sonography was performed prior to curettage to delineate polyp. Mindray's transabdominal ultrasound probe (5–7.5 hertz) was placed on the patient's abdomen to visualize the uterus. Dilatation and curettage were performed under ultrasound guidance. SIS was repeated to ensure complete removal of the polyp (Izhar's Modification for removal of polyp). Sexual contact was encouraged, and woman was requested to report back if she becomes pregnant. Then, a transvaginal scan was done to confirm a fetal heart beat.

Follow up

All women with polyps, whether they requested removal or not, were followed for a period of twelve months. The follow up was maintained via telephone calls and repeated transvaginal scans at 3, 6, 9 and 12 months. Those who did not comply with the follow up, were not included in the final statistical analysis. Those with recurrence of polyps were planned to have removal and follow up adjusted.

The primary outcome measure was women who had clinical pregnancy i.e. fetal heartbeat present on transvaginal scan after they had β-hCG positive in serum during the follow up period.

All participants provided informed consent. In lieu of formal ethics committee or formal institutional review board approval, Helsinki's declaration was followed. No subjects were harmed, confidentiality was maintained, and no subject was enrolled in the study without formal informed consent.

Statistical analysis

The Quantitative variables duration of infertility and duration from treatment to conception were presented by means and standard deviation. The t-test for two independent samples was used to compare means for both groups; those requesting removal and those not requesting removal. Frequency and percentages were computed for qualitative variables; type of infertility and conception. Chi square test was used to compare groups.

Survival analysis was performed to evaluate the probability of conceiving in both groups. Curves were compared by the means of Mantel Haenszel log-rank test for categorical variable, which in this case was conception. The effect of independent variables age, duration of infertility, position of polyp, polypectomy and type of infertility on conception was estimated using Cox' proportional hazard model. The hazard ratios were calculated with a confidence interval of 95%. Analyses were performed using SPSS version 15.0 statistical package (SPSS, Inc.,) with statistical significance denoted by a p value of less than 0.05.

Results

There were 950 women with unexplained infertility who were recruited for saline sonography. Out of them, 213 had polyps that did not regress on a 6 weeks' and a 12 weeks' scan. This gave a polyp prevalence of 22.4% in the study population.

Of the 213 with polyps, 103 agreed to undergo polypectomy after counselling and were labeled as cases. 110 women with polyps refused to undergo the intervention and were labeled as controls.

Out of the 103 cases 8 were lost to follow up and 3 polyps were not confirmed on histopathology and were excluded from the analysis. So, this left us with 92 cases that were taken into consideration. There were no recurrences in the intervention group during the study period. Out of the 110 controls, 18 did not comply with the follow up and were thus not included in the final analysis. The remaining 92 cases were taken into account (Fig. 1).

Table 1 shows the comparison between the two groups. Both groups were similar in terms of the mean age (p = 0.060) and mean duration of infertility (p = 0.316). There was no statistical difference in the position of a polyp (p = 0.157) and type of infertility (p = 0.282) between the two groups. The mean time to conception for cases was 9.26 ± 3.928 months and for controls – 11.33 ± 2.07 months, which was statistically significant (p <0.001). The primary outcome measure was women who had a clinical pregnancy i.e. had β-hCG positive in serum during the follow up period. During the study period, 37 (40.2%) cases and 10 (10.9%) controls conceived, showing that polypectomy significantly affected the conception (p <0.001).

Survival analysis showed a statistically significant difference in pregnancy rate following polypectomy between the two groups (log rank, p <0.001) (Fig. 2).

The effects of various variables on pregnancy rate were estimated using Cox' proportional hazards model analysis (Tab. 2).

The results showed that age and type of infertility did not significantly appear to influence the pregnancy rate. The duration of infertility ($p = 0.007$), the position of a polyp ($p = 0.049$) and polypectomy ($p < 0.001$) influenced pregnancy rate, though.

Discussion

Main findings

The present study evaluates the effect of polypectomy on the clinical pregnancy rate in women with unexplained infertility. Our study shows that polypectomy increases the odds of conception in these women.

The mean time to conception for cases was lesser than the time for controls.

The cumulative pregnancy rate in the polypectomy group was also higher than the one of the controls.

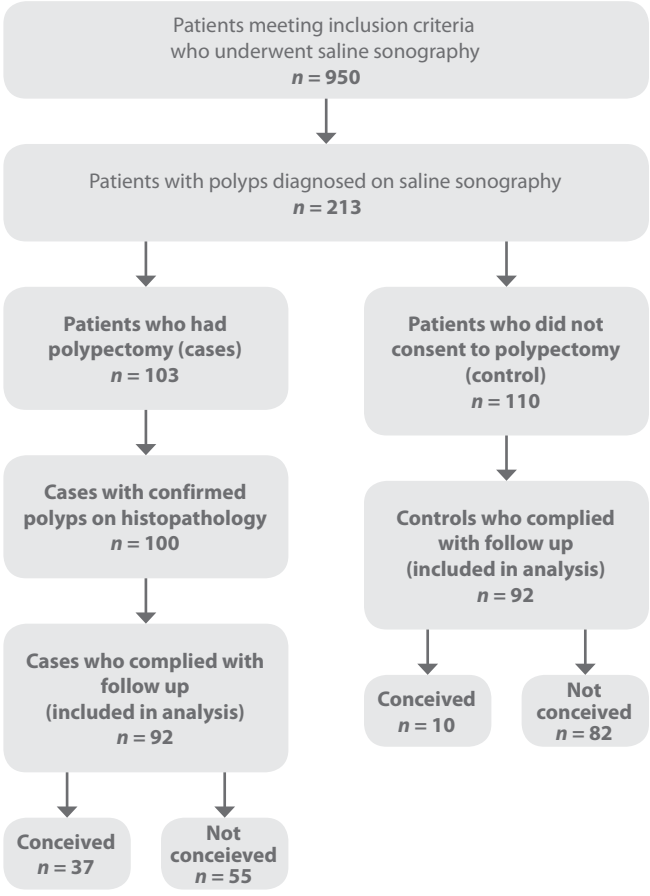

Fig. 1. *Profile of the study*

Tab. 1. *Comparison between cases and controls*

Characteristic	Polyp removed n = 92 (%)	Not removed n = 92 (%)	p value
Age in years†	30.13 ± 3.430	29.27 ± 2.685	0.060‡
Duration of infertility in year†	4.59 ± 2.001	4.32 ± 1.65	0.316‡
Time to conception in months†	9.26 ± 3.928	11.33 ± 2.07	<0.001‡
Conception			<0.001*
Yes	37 (40.2%)	10 (10.9%)	
No	55 (59.8%)	82 (89.1%)	
Position of polyp			0.157*
Fundal	45 (48.9%)	38 (41.3%)	
Anterior	16 (17.4%)	18 (19.6%)	
Posterior	24 (26.1%)	34 (37.0%)	
Midcavity	7 (7.6%)	2 (2.2%)	
Type of infertility			0.282*
Primary	77 (83.7%)	82 (89.1%)	
Secondary	15 (16.3%)	10 (10.9%)	

* The Chi-square statistic is significant at the 0.05 level
† T-test statistic is used for quantitative variables
‡ T-test statistic is significant at 0.05 level

The duration of infertility, the position of a polyp and polypectomy influenced pregnancy rate, whereas age and type of infertility did not have a significant influence.

Strength and limitations

The strength of the study is that it assesses the role of polypectomy as the sole intervention for improving clinical pregnancy rate in women with unexplained infertility. Contrary to the contemporary studies, our women did not undergo artificial reproductive technologies so the results can be attributed to polypectomy alone.

Previous studies used blind curettage whereas we used ultrasound guidance to locate polyp during curettage. We feel that under guidance, curettage is no longer a blind procedure. Moreover, the cavity was reviewed immediately after curettage to look for the pieces of polyps. When visualized, curettage was performed on identified uterine segments. SIS was repeated again to confirm the complete removal of the polyp. It was cumbersome but ensured complete removal. To our knowledge and literature review this is a novel practice and we would like to coin this as 'Izhar Modification'.

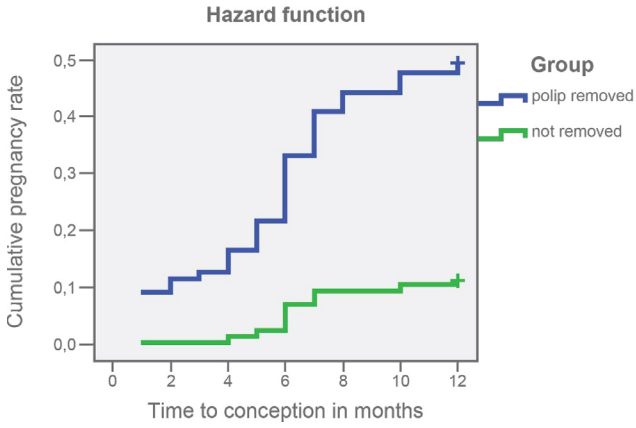

Fig. 2. *Kaplan Meier survival curve of women who conceived during the follow up (log rank test,* p *<0.001)*

We did not follow the patients who had fetal heart beat on transvaginal scan to ascertain the outcome of pregnancy so this aspect needs further evaluation through larger trials.

The study does not compare the guided removal of polyps with Hysteroscopic removal. This also needs to be elucidated, an equivalence can serve the low resource settings immensely.

Interpretation

The favorability of uterine endometrium is crucial for embryo implantation. Minor abnormalities such as polyps also affect receptivity of endometrium and can adversely affect fertility[10].

In women with unexplained infertility, endometrial polyps are identified with hysteroscopy in 16.5% to 26.5% of cases[11]. In our study, endometrial polyps were identified in 22.4% women with unexplained infertility on saline sonography, which is in agreement with the prevalence reported worldwide[12].

Age of the woman and duration of infertility are considered major factors affecting conception. In our analysis age was negatively correlated with conception, hazard ratio 0.993 (95% CI 0.907–1.088), but it did not reach statistical significance.

Women with unexplained infertility have a cumulative pregnancy rate of 28% over 7 to 9 years[13]. Our analysis also predicted a positive correlation between conception and duration of infertility, hazard ratio of 1.244 (95% CI 1.060–1.460). This confirms that odds of pregnancy increase over time and patients may benefit from conservative management in certain select cases.

The position and size of a polyp suitable for polypectomy have constantly been a concern to experts worldwide. Studies report that polypectomy offers an advantage over conservative management irrespectively of size and position of polyps[14]. In a retrospective study analyzing the impact of the position of a polyp on fertility (n = 230), pregnancy rate after polypectomy at utero-tubal junction was significantly higher than that of other locations. The pregnancy rate after surgery was as follows, by location: uterotubal junction, 57.4%; posterior uterine wall, 28.5%; anterior uterine wall, 14.8 %[15]. Similarly, in our analysis pregnancy rate was highest for polypectomy at uterotubal junction. The pregnancy rates after surgery were as follows for our study: fundal, 63.8%; posterior uterine wall, 19.1%; anterior uterine wall, 14.9% and midcavity 2.1%

Our analysis also predicts that women with polyps at fundus are 4.9 times more likely to conceive after polypectomy when compared to women with polyps in midcavity. This supplements the fact in aforementioned studies that polyps hindering transport of ovum to cavity can be a cause of infertility in these women.

Our study showed that the position of a polyp is a factor affecting cumulative pregnancy rate but the significance is questionable (p = 0.049), perhaps a larger sample size can answer the question more accurately.

Hysteroscopic polypectomy has shown to enhance the pregnancy rate in several retrospective and prospective analyses[16]. In their randomized controlled trial, Perez Medina concluded that polypectomy increased the relative risk of pregnancy 2.1 times and should be considered prior to artificial reproductive techniques in women with endometrial polyps[9]. Our analysis showed that hazard ratio for conception was 4.312-fold (95% CI 2.112–8.803) after polypectomy in women with otherwise unexplained infertility which is as predicted by previous studies. The aspect that we want to highlight is that women conceive spontaneously after polypectomy emphasizing a significant role of polyps in this population of infertile women. We did not resort

Tab. 2. *Factors affecting the clinical pregnancy rate*

Characteristics	Hazards ratio (95% CI)	*p* value
Duration of infertility	1.244 (1.060; 1.460)	0.007*
Polypectomy	4.312 (2.112; 8.803)	<0.001*
Position of polyp		0.049*
Fundal	4.914 (0.665; 36.301)	
Anterior	2.704 (0.331; 22.079)	
Posterior	1.989 (0.249; 15.893)	
Midcavity	Reference	
Age	0.993 (0.907; 1.088)	0.884
Infertility type	1.260 (0.486; 3.271)	0.635
–2 log likelihood	469.299	
Model chi square	34.853*	
Degrees of freedom	7	
* The Chi-square statistic is significant at the 0.05 level		

to any artificial reproductive technology and the patients conceived spontaneously.

Perez Medina also contemplated that there was a strong cause-effect of polyp in implantation and many women conceived spontaneously after polypectomy. They deferred first cycle of IUI to three menstrual cycles after polypectomy. In their analysis, 65% of women who underwent polypectomy conceived before their first cycle and the other 35% over 4 cycles of IUI[9]. In our study, patients did not undergo any artificial reproductive technology and were followed for 12 months. The time to conception was significantly lower for women who chose polypectomy. The mean time to conception for cases was 9.26 ± 3.928 months and for controls – 11.33 ± 2.07 months. The difference was most notable in the initial 3 months and then peaked again 6 months after polypectomy.

The type of infertility, primary or secondary, affects chances of conception. In our analysis, women with primary infertility and endometrial polyps were more likely to conceive than women with secondary infertility. The strength of the association on Cox regression did not reach statistical significance. This is in contrast to the findings that pregnancy rate is not influenced by the type of infertility[14,17].

Another aspect that warrants discussion is that the guided removal of polyps followed by confirmation of complete clearance by SIS was an innovation (Izhar's Modification), made to substitute hysteroscopy in low resource setting. Separate trials are needed to establish/compare its efficacy with hysteroscopy. Studies comparing SIS with diagnostic hysteroscopy have confirmed that SIS is a reliable alternative[18,19]. We see no reason for which it should not detect residual polyps on scanning after ultrasound guided D &C.

Positive effects of endometrial damage as in the case of endometrial scratching on pregnancy rates are being reported. Some of these unexplained cases might be due to local immune reaction[20]. A cause effect relationship in this regard is difficult to deny. Our study included patients with polyps and an obvious cause acting as a natural intrauterine contraceptive device cannot be ignored. An adjustment for polyps could have been possible if the study included women with unexplained infertility without polyps.

Conclusion

Our study shows the beneficial effect of removal of polyps in women with unexplained infertility. Women are four times more likely to conceive spontaneously after polypectomy.

We propose that polypectomy should be considered in all women with unexplained infertility as removal can substantially improve pregnancy rate. Large multi-centered randomized controlled trials are needed to assess the effect of polypectomy alone on the conception rate in women with unexplained infertility.

Conflicts of interests

The authors have no conflicts of interest to disclose.

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