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## **Endometrial Polyps and Subfertility**

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Ertan Saridogan and Ali Al Chami have no conflict of interest.



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## Endometrial Polyps and Subfertility

### Abstract:

Endometrial polyps are frequently seen in subfertile women and there is some evidence suggesting a detrimental effect on fertility. How polyps contribute to subfertility and pregnancy loss is uncertain and possible mechanisms are poorly understood. It may be related to mechanical interference with sperm transport, embryo implantation, or through intrauterine inflammation or altered production of endometrial receptivity factors. Different diagnostic modalities such as 2- or 3-dimensional transvaginal ultrasound, saline infusion sonography or hysteroscopy are commonly used to evaluate endometrial polyps with good detection rates. The approach of clinicians towards polyps detected during infertility investigations is not clearly known and it is quite likely that there is wide variation amongst different groups. Most clinicians suggest hysteroscopy and polyp removal if a polyp is suspected before stimulation for in vitro fertilisation or a frozen embryo transfer cycle. However, the clinical evidence and benefit of different management options during assisted reproduction technology cycles are conflicting. Currently, there is insufficient evidence to recommend one particular option over others when a polyp is suspected during stimulation for IVF. A properly designed randomized controlled trial is needed to determine the best treatment option.

In this article we present the available evidence and our practice related to different diagnostic modalities and management options. We also discuss the available literature relevant to the management of endometrial polyps in relation to natural conception, intrauterine insemination, and in vitro fertilization.

**Key words:** Endometrial polyps, infertility, ultrasound, hysteroscopy, in vitro fertilisation

1 Endometrial polyps are focal growths of the uterine mucosa and consist of  
2 endometrial glands, stroma and blood vessels. It is estimated that uterine polyps are  
3 found in 10% of general female population [1]. Whilst they may be asymptomatic,  
4 polyps are commonly identified during investigations for abnormal uterine bleeding  
5 and infertility. Abnormal uterine bleeding is the most common symptom of  
6 endometrial polyps, and in women with such bleeding, the prevalence of endometrial  
7 polyps is thought to be between 20-30% [2, 3, 4].  
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19 In subfertility patients the diagnosis of endometrial polyps is frequently an incidental  
20 finding. The association between endometrial polyps and subfertility is controversial,  
21 as many women with polyps have successful pregnancies. However, recently there  
22 has been an accumulation of publications in the literature suggesting that the polyps  
23 are indeed relevant to fertility and fertility treatment outcome. In this article, we give  
24 an overview of epidemiology, diagnosis and management of polyps in subfertile  
25 population and discuss possible mechanisms how polyps may affect fertility.  
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### 39 **Prevalence of endometrial polyps in infertile women**

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41 Since transvaginal ultrasound examination (TVUS) has become a standard part of the  
42 gynaecological assessment, and saline infusion sonography or hysteroscopy are often  
43 performed if intrauterine mass lesions are suspected, polyps are more frequently  
44 detected. This approach has led to an increase in the diagnosis of endometrial polyps  
45 in subfertile and otherwise asymptomatic patients.  
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53 Polyps are considered amongst factors that might contribute to infertility and  
54 recurrent pregnancy loss. It has been postulated that congenital uterine anomalies and  
55 acquired structural cavitary defects such as leiomyomas, polyps, and synechiae might  
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1 have negative impact on endometrial receptivity and thus implantation failure. This  
2 presents a major clinical challenge and is a cause of considerable stress to patients.  
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4 The prevalence of such unsuspected intrauterine abnormalities, diagnosed by  
5 hysteroscopy prior to IVF, has been described to be between 11 to 45% [5, 6, 7].  
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7 Endometrial polyps are the most commonly reported uterine structural abnormalities.  
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9 Whilst one study [5] identified polyps in 32% of patients (323/1000) undergoing IVF,  
10 another [6] showed 41(6%) patients with polyps in a similar patient population of 678  
11 asymptomatic IVF patients. Endometrial polyps also appear to be the most commonly  
12 detected abnormality (16.7%) in patients with recurrent implantation failures after  
13 IVF [6]. It is suggested that polyps have higher incidence in women with  
14 endometriosis (46.7%), although this high figure has not been reported by other  
15 groups [8].  
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### 31 **Possible mechanisms of polyp-subfertility association**

32 How polyps contribute to subfertility and pregnancy loss is uncertain and the  
33 mechanism is poorly understood. It may be related to mechanical interference with  
34 sperm transport, embryo implantation, or through intrauterine inflammation or  
35 increased production of inhibitory factors such as glycodeilin.  
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43 In a retrospective study involving 230 subfertile women undergoing hysteroscopy and  
44 polypectomy, Yanaihara et al. concluded that the location of the endometrial polyp  
45 may influence spontaneous pregnancy rates and fertility outcome. The pregnancy rate  
46 within six months after surgery was 57.4% for polyps located at the utero-tubal  
47 junction, 40.3% for multiple polyps, 28.5% for posterior wall polyps, 18.8% for  
48 lateral wall polyps and 14.8% for anterior uterine wall polyps [9]. These results  
49 suggest that the mass of polyps may interfere with the reproductive processes such as  
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1 sperm transport, embryo implantation or early pregnancy development. Conversely, in  
2 another retrospective study 83 subfertile women with a history of menstrual disorder,  
3 hysteroscopic polypectomy appeared to improve fertility and pregnancy rates  
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5 irrespective of the size or number of the polyps. In particular, there was no difference  
6  
7 in pregnancy or miscarriage rates between women who had polypectomy for a small  
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9 ( $\leq 1$  cm ) and those who had surgery for a bigger or multiple polyps [10]. Lack of  
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11 association between the size of polyps and fertility outcomes goes against a  
12  
13 mechanical effect, as a bigger effect would be expected in the presence of larger  
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15 polyps.  
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19 Glycodelin, a glycoprotein, has been shown to inhibit sperm-oocyte binding and NK  
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21 cell activity. In ovulatory human endometrium, glycodelin levels are very low  
22  
23 between 6 days before, and 5 days after ovulation (peri-ovulatory period). Low  
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25 glycodelin levels may facilitate fertilisation and then the levels increase significantly  
26  
27 6 days after ovulation to suppress NK cell activity and render the endometrium  
28  
29 receptive to implantation. It is speculated that fertilisation and endometrial receptivity  
30  
31 may be altered by increased glycodelin production in the uterine cavity of patients  
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33 with leiomyomas and polyps at the time (peri-ovulatory) when uterine glycodelin  
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35 levels should be absent or low [11].  
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39 It is also suggested that the presence of polyps may alter *HOXA10* and *HOXA11* gene  
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41 expression, established molecular markers of endometrial receptivity, and thus impair  
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43 endometrial receptivity in uteri with polyps [12].  
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### 53 **Diagnosis:**

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55 The diagnostic modalities that are commonly used to evaluate endometrial polyps  
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57 include a 2- or 3-dimensional transvaginal ultrasound, best performed in the early  
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1 proliferative phase of the menstrual cycle, saline infusion sonography, and  
2 hysteroscopy. The diagnostic accuracy of 2-D TVUS is relatively poor compared with  
3 other diagnostic modalities such as saline infusion sonography (SIS) or hysteroscopy.  
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5 An endometrial polyp is suspected by the presence of a hyperechogenic endometrial  
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7 mass (Figure 1).  
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11 Performing the ultrasound examination in early proliferative phase, when the  
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13 endometrium is thin, makes it easier to see the polyp. Sessile polyps can be confused  
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15 by submucous fibroids. It might also be difficult to distinguish between a true polyp  
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17 and polypoid endometrium by ultrasound, especially after superovulation, which  
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19 tends to cause a thick proliferative endometrium.  
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23 In one study hysteroscopy confirmed the ultrasound findings in 90% of cases [13].  
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25 Fatemi et al [6] identified polyps hysteroscopically in 41 out of 678 unselected,  
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27 asymptomatic, infertile women with a normal transvaginal scan. In our practice we  
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29 perform 3D imaging (Fig 2) of the uterus as a routine during baseline ultrasound scans  
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31 with the aim of improving diagnostic accuracy [14].  
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35 A systematic review and meta-analysis suggested that saline infusion sonography has  
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37 a high degree of diagnostic accuracy in the detection of all types of intrauterine  
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39 abnormalities with a sensitivity and specificity of 88% and 94% respectively. The  
40  
41 diagnostic accuracy of SIS remained high when analyzed separately for individual  
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43 pathologies such as endometrial polyps, submucous myomas, intrauterine adhesions  
44  
45 and congenital uterine anomalies. It is also suggested that SIS can be considered as  
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47 an alternative to hysteroscopy as the specificity reaches close to 100% in detecting  
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49 intrauterine adhesions, uterine anomalies, endometrial polyps and submucous  
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51 myomas [15].  
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1 Hysteroscopy remains the gold standard in the diagnosis of endometrial polyps (Fig  
2 3). Besides, hysteroscopy allows simultaneous treatment in the form of removal of the  
3 endometrial lesions such as polyps and small submucous fibroids.  
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9 In our practice we carry out a 2D- and 3D- TVUS as a baseline investigation. If  
10 TVUS is suggestive of endometrial polyps we perform a hysteroscopy, usually as an  
11 outpatient procedure, depending on the patient's preference. If the TVUS is  
12 inconclusive in an infertile and otherwise asymptomatic woman, we perform 3D  
13 saline infusion sonography (3D-SIS).  
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## 24 **Management**

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29 The approach of clinicians towards polyps detected during infertility investigations is  
30 not clearly known and it is quite likely that there is wide variation amongst different  
31 groups. The majority of published data recommend removal of polyps, but this may  
32 be due to publication bias, as groups who do not routinely look for polyps may be less  
33 likely to publish data on impact of polyps or polyp removal. Some endometrial polyps  
34 may resolve spontaneously, as regression has been observed in 27% of cases [16].  
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45 Endometrial polyps are usually removed as part of a hysteroscopic procedure;  
46 removal may be either a blind procedure using a curette or polyp forceps after  
47 hysteroscopic diagnosis, or may be under direct vision using operative  
48 minihysteroscopes or resectoscopes. Published surveys suggest differences of practice  
49 in different countries. In the Netherlands, the majority of clinicians appear to remove  
50 polyps under direct vision either in the outpatients or under general anaesthesia [17,  
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18]. In contrast, the preference of clinicians in the United Kingdom was blind avulsion or curettage after hysteroscopic location [19]. These surveys also indicated that the clinicians were more likely to perform these procedures in the outpatient setting at university teaching hospitals, whereas general anaesthetic procedures were more likely in general hospitals.

Historically, it is believed that 10% of intrauterine lesions, mainly polyps, are missed during 'blind' curettage [20]. For this reason, hysteroscopy-directed polypectomy using scissors, a loop electrode, electric probe, or a morcellator is recommended to minimize damage to the surrounding endometrium and to ensure the polyp has been removed in its entirety. The resectoscope appears to be the method of choice and with least recurrence rate compared to electric probe, microscissors, and grasping forceps [21].

Our practice is to carry out the majority of polyp removals in the outpatients as 'see and treat' procedures under direct vision using bipolar electrodes and/or mechanical biopsy forceps [22]. An economic analysis of this approach suggests that this is more cost effective to the health service compared to routine general anaesthetic procedures [23].

**Outcome:**

1 A number of publications indicate that removal of endometrial polyps is beneficial for  
2 natural conceptions [24], intrauterine insemination [25] and assisted reproduction  
3 technologies (ART).  
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10 Natural conception  
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14 Three nonrandomized studies found an association between polypectomy and  
15 improved spontaneous pregnancy rates. Varasteh et al [24] studied infertile women  
16 with and without endometrial polyps and found a pregnancy rate of 78.3% after  
17 polypectomy compared with 42.1% in those with normal uterine cavity.  
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21 Spiewankiewicz et al. [26] reported a pregnancy rate of 76% where 19 out of 25  
22 infertile patients conceived within 12 months after polypectomy, whereas Shokeir et  
23 al. [27] reported a 50 % pregnancy rate after polypectomy in such patients. These  
24 studies suggest women with otherwise unexplained infertility may benefit from  
25 polypectomy.  
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39 Intrauterine insemination  
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43 Perez-Medina et al. randomized 215 infertile women, with ultrasonographically  
44 diagnosed endometrial polyps undergoing IUI, to either hysteroscopic polypectomy in  
45 the study group or diagnostic hysteroscopy and polyp biopsy in the control group.  
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47 Patients who underwent hysteroscopic polypectomy had a better possibility of  
48 becoming pregnant after polypectomy, with a relative risk of 2.1(95% confidence  
49 interval 1.5-2.9) [25].  
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1 In another study 120 infertile patients planned to have IUI and diagnosed with  
2 endometrial polyps were randomly allocated either to hysteroscopic polypectomy or  
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4 no intervention. All patients were scheduled to receive four cycles of IUI. The  
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6 cumulative pregnancy rates were significantly higher in the study group (38.3% vs  
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8 18.3%;  $p=0.015$ ) suggesting that hysteroscopic polypectomy prior to IUI is an  
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10 effective measure and improves pregnancy rates [28].  
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### 17 Endometrial polyp management and IVF

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22 When suspected by ultrasound prior to commencement of stimulation for in vitro  
23 fertilization (IVF) or prior to frozen embryo transfer (FET), polyps are usually further  
24 investigated and treated. However, the management of polyps found incidentally  
25 during the course of stimulation for IVF is controversial. Treatment options include  
26 continuation of ovarian stimulation followed by fresh transfer, freezing all embryos  
27 and replacement of frozen-thawed embryos after removal of the polyp, or cancellation  
28 of the treatment cycle and removal of the polyp. The factors that affect decision  
29 making include the number of embryos created, previous reproductive history, and the  
30 success rate of the FET program, as well as the clinicians' preference.  
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46 Lass et al. examined the effect of polyps on 83 women with ultrasonographically  
47 identified polyps < 2 cm and divided them in two groups before oocyte retrieval  
48 during IVF. Forty-nine women completed the standard IVF and embryo transfer  
49 treatment and 34 women underwent hysteroscopic polypectomy immediately after  
50 oocyte retrieval and the embryos were cryopreserved and transferred in a subsequent  
51 cycle. No statistically significant difference was observed in pregnancy rates between  
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1 the two groups and compared with the overall pregnancy rate for their clinic during  
2 the same period of time. There was a trend toward increased pregnancy loss in the  
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5 fresh embryo transfer group [13].  
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9 Another study assessed the effect of endometrial polyps < 1.5 cm in size on  
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11 intracytoplasmic sperm injection (ICSI) cycles. Patients were divided into three  
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13 groups: patients with endometrial polyps discovered during ovarian stimulation  
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15 (n=15), patients who underwent hysteroscopic polyp resection prior to ICSI cycle  
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17 (n=20) and patients without polyps (n=956). There pregnancy rates were 53.3%,  
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19 45.0%, and 40.1%, respectively. There was no statistical difference in pregnancy and  
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21 implantation rates between the three groups [29].  
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29 The effect of hysteroscopic polypectomy on IVF outcome without cycle cancellation  
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31 was assessed in a case series of six patients who underwent hysteroscopic  
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33 polypectomy on days 7 and 9 with a wire-loop without use of electric current during  
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35 an IVF cycle. A 50% pregnancy rate was observed suggesting hysteroscopic  
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37 polypectomy may not be detrimental to IVF cycle outcome [30].  
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44 Tiras et al. assessed the effect of polyps, less than 1.5 cm in size, diagnosed before or  
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46 during ICSI. Group 1 (n=47) were patients diagnosed with an endometrial polyp and  
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48 had hysteroscopic polypectomy before stimulation. These were compared with 47  
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50 matched control patients without endometrial polyps who underwent standard ICSI  
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52 cycle (Group 2). Group 1 patients had live birth rates similar to their controls (Group  
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54 2) (25.5% vs 31.9%). This study also examined 128 patients (Group 3) diagnosed  
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56 with an endometrial polyp during stimulation in their ICSI cycle. Group 3 was  
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1 compared to with 128 match control patients without endometrial polyps who  
2 underwent standard ICSI cycle (Group 4). Groups 3 and 4 also had similar live birth  
3 rates (40.6 vs 39.8). This retrospective study suggests that patients with an  
4 endometrial polyp detected and resected before ICSI cycle had similar pregnancy  
5 rates compared with patients with no endometrial polyps. It also proposes that for  
6 endometrial polyps diagnosed during stimulation and < 1.4 cm in size, it is not  
7 necessary to intervene or cancel the embryo transfer [31].  
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19 In our practice we usually perform 3D SIS routinely before IVF cycles with fresh or  
20 frozen embryo transfer. This makes it very unlikely to diagnose polyps during  
21 stimulation. In general we recommend hysteroscopic polypectomy for polyps  
22 diagnosed before stimulation. If we diagnose a polyp during stimulation we counsel  
23 our patients and discuss different options of treatment based on available evidence.  
24 We don't usually consider polypectomy during stimulation taking into consideration  
25 the potential harmful effect of such a procedure just before embryo transfer. With the  
26 current advances in embryo freezing and the frozen embryo transfer cycles outcome,  
27 which is higher than fresh embryo transfer in our unit , we tend to freeze all embryos  
28 after egg collection and plan for a hysteroscopic polypectomy followed by a frozen  
29 embryo transfer cycle.  
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## 51 **Conclusion**

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55 Endometrial polyps are commonly seen in subfertile women and there is some  
56 evidence suggesting a detrimental effect of polyps on fertility. Use of appropriate and  
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sensitive diagnostic tests for subfertility and prior to fertility treatment is commonly performed with good detection rates. The limited data available on removal of polyps on spontaneous pregnancy and intrauterine insemination success rates suggest a potential benefit. Most clinicians suggest hysteroscopy and polyp removal if a polyp is suspected before stimulation for IVF or a frozen embryo transfer cycle. However, the clinical evidence and benefit of different management options during ART cycles are conflicting. Currently, there is insufficient evidence to recommend one particular option over others when a polyp is suspected during stimulation for IVF. A properly designed randomized controlled trial is needed to determine the best treatment option.

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### Figure Legends

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**Fig.1 a:** A transvaginal ultrasound scan 2D image showing a fundal polyp (arrow); **b:** A polyp filling the cavity (arrow)

**Fig.2** 3D US appearance of an endometrial polyp (arrow)

**Fig. 3 a:** Hysteroscopy image showing a left lateral wall polyp; **b** Multiple polyps within the uterine cavity

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