Endometrial Polyps in Reproductive-Age Fertile and Infertile Women

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Key words: endometrial polyp, infertility, sonohysterography, reproductive age, fertile, endometriosis

Abstract

Endometrial polyps are a frequent finding in infertile patients. Little is known about the true prevalence of polyps in infertile patients. It is unproved whether polyps are causative of infertility, or whether surgical polypectomy by hysteroscopy improves the likelihood of successful conception. This article reviews endometrial polyps in reproductive-age fertile and infertile women.

IMAJ 2006;8:192–195

Endometrial polyps, submucosal fibroids, and intrauterine synechiae are prevalent in infertile women [1,2]. The current treatment philosophy of infertility, particularly in those women undergoing in vitro fertilization and embryo transfer, is to perform hysteroscopic corrective surgery when intrauterine filling defects are diagnosed. There is reasonable evidence to claim this as a prudent management approach for submucosal leiomyomata, since pregnancy rates are decreased in the presence of submucosal fibroids and corrective surgery improves the likelihood of pregnancy [3]. It has not been proved whether polyps are more common in infertile women compared with non-infertile women, whether there is a difference in prevalence depending upon the etiology of the couple's infertility, or whether there is an age threshold below which polyps are uncommon in infertile women. It is also not known whether polyps are causative of infertility, or whether surgical polypectomy by hysteroscopy improves the likelihood of successful conception.

The etiology of endometrial polyps

The etiology of endometrial polyps is believed to be related to estrogen stimulation [4]. In susceptible individuals, ongoing stimulation by estrogen and/or unopposed estrogen could conceivably result in hyperplasia, adenomatous hyperplasia, atypia, and even malignancy. Since all women of reproductive age experience significant exposure to estrogen, it is unclear what renders some individuals susceptible to polyp formation. An association between endometrial polyps and tamoxifen use has been noted [5], presumably due to tamoxifen's estrogenic actions on the endometrium. An association has been suggested between endometriosis and the presence of polyps or polypoid endometrium [6]. A recent study found that uterine flushings and plasma of women with polyps contained elevated levels of the endometrium-derived protein glycodelin when compared to control women without polyps [7]. Glycodelin is an angiogenic factor and could plausibly play a role in the genesis of endometrial polyps by promoting neovascularization. Most polyps originate in the uterine fundus [8,9].

Prevalence and incidence

The prevalence of endometrial polyps depends upon the population being studied. Using saline infusion sonohysterography, the incidence of endometrial polyps in asymptomatic premenopausal women older than 30 has been reported to be 10% [10]. The majority of these were found in women older than 35; only 3% of polyps in that series were seen in women under the age of 35 [10]. In one series, 13% of perimenopausal women with abnormal uterine bleeding had polyps [11], and another series of 114 women aged 25–69 reported the presence of endometrial polyps in 35% with abnormal uterine bleeding [12]. At autopsy, 10% of uteri contain polyps [9]. Polyps occur in all age groups but are most commonly found in women between age 40 and 49 [8]. Notably, the majority of polyps (4/7, 57%), particularly smaller polyps (average diameter 0.7 cm vs. 1.3 cm), in asymptomatic premenopausal women appear to regress spontaneously [13].

Relationship to infertility

The prevalence of polyps in the infertile population has not been studied in detail. In a retrospective analysis of more than 5700 IVF cycles at Bourne Hall, baseline and follicle-monitoring transvaginal ultrasound uncovered suspected polyps in 83 cycles (1.4%), and in the women with suspected polyps who chose to be evaluated hysteroscopically, approximately 90% were confirmed to have polyps or polypoid endometrium [14]. Transvaginal ultrasound is not as sensitive as SIS or hysteroscopy in detecting intrauterine defects [15], which may account in part for the low incidence of polyps detected. It has been suggested that the type of hysteroscopic distension medium and/or hysteroscopic technique used may influence the surgeon's perception of intrauterine filling defects. An incidence of 15.6% of endometrial polyps (35/235) detected hysteroscopically was found in a eu-

IVF = in vitro fertilization
SIS = saline infusion sonohysterography

menorrheic infertile population, and diagnostic hysteroscopy was recommended by the authors as a part of routine workup of infertile woman [16]. Taylor and colleagues [2] reported that 29% of women with primary infertility and 41% of women with secondary infertility had filling defects (polyps, fibroids, adhesions, septae) when dextran 70 was used, vs. only 6–11% when CO_2 was used. They surmised that since the dextran 70 hysteroscope required dilatation prior to insertion, whereas the CO_2 hysteroscope did not, that trauma from dilation was responsible for artifactual findings. It is notable that the prevalence of polyps using dextran 70 was 12% in both the primary and secondary infertility groups, an incidence not different to that of a control group of patients hysteroscoped prior to tubal reversal, and not greater than the prevalence reported in autopsy studies [9]. The prevalence of polyps using the CO_2 hysteroscope was less than 2%.

A trend toward increased miscarriages in patients with "suspected" polyps undergoing IVF-ET compared to women with no suspicion of polyps was suggested by the Bourne Hall group. In their series, 3 of 27 clinical pregnancies (27.3%) in the "suspected" polyp group miscarried, compared with 113/597 (10.7%) of all clinical pregnancies over the same period. There was no difference in clinical pregnancy rate between the "suspected" polyp group (11/49 cycles, 22.4%) compared with the rate for all cycles (597/4493, 22.3%) [14].

Varasteh and co-workers [17] looked retrospectively at 78 women who attempted to conceive after hysteroscopic evaluation and resection of polyp or fibroid, if found. The study spanned 21 years, from 1975 to 1996. They documented an enhanced pregnancy rate in infertile women post-polypectomy compared with infertile women with normal endometrial cavities [17]. Whether or not co-treatments were undertaken was not documented, and the time interval of the study encompassed the pre-IVF, pre-superovulation/intrauterine insemination era. In a prospective, randomized study Perez-Medina et al. [18] examined whether hysteroscopic polypectomy before intrauterine insemination achieved better pregnancy outcomes than no intervention. In the study group, hysteroscopic polypectopy was performed after sonographic diagnosis of endometrial polyp. Women in the study group were found to have a better chance of becoming pregnant after polypectomy (relative risk 2.1), and pregnancies after polypectomy were frequently obtained spontaneously while waiting for treatment. Preutthipan and Herabutya [19] showed in a retrospective study that restoration of reproductive ability did not depend on the size of the removed polyp. The management choices for endometrial polyp diagnosed in patients undergoing IVF treatment are: cryopreservation, cycle cancellation, embryo transfer, and polypectomy preceding oocyte retrieval [20].

Theorized mechanisms by which polyps could adversely affect reproductive performance include: irregular intra-endometrial bleeding; creation of an inflammatory endometrial response; similar to an intrauterine device; an obstructive defect inhibiting sperm transport; a physical surface area effect preventing exposure of the embryo to the endometrium; and an endocrine surface area effect in which increased endometrium surface area (from both the polyp and the endometrial lining) results in increased secretion of glycodelin [7], which has been shown to inhibit sperm binding to the zona pellucida [21].

IVF-IT = IVF-embryo transfer

Relationship to endometriosis

A retrospective study found endometriosis in 27 of 32 women (84%) with polyps or polypoid endometrium at hysterosalpingography, compared with endometriosis in only 19 of 88 patients (22%) without polyps or polypoid endometrium [6]. It was suggested that the presence of polyps may explain the menstrual disturbances observed in many women with endometriosis.

Properly designed future randomized controlled trials are needed to test the efficacy of surgical intervention

Tamoxifen

There is an association between tamoxifen use, endometrial polyp formation, and endometrial carcinoma. One series reported that 27% of women treated for breast cancer with tamoxifen had polyps on SIS [22], but the prevalence of polyps prior to treatment was not determined in that series. The pretreatment prevalence of polyps in another series of breast cancer patients prior to tamoxifen therapy was approximately 13% [23].

Malignancy

The likelihood of an endometrial polyp harboring malignancy is small, even with symptomatic irregular bleeding. The lifetime risk of developing adenocarcinoma of the endometrium is 2–3%. This is higher in obese women with unopposed estrogen, such as polycystic ovarian syndrome. The peak incidence of the disease occurs in the late fifties to early sixties [24]. In one series, only 5% of all women who developed endometrial adenocarcinoma were under the age of 40 [25]. In a cohort of 1270 young women with chronic anovulation, a subsequent malignancy developed in 30 (2.4%) compared with an expected number of 29.8. The relative risk of developing adenocarcinoma of the endometrium with chronic anovulation in this series was 3.1 (95% confidence interval 1.1–7.3) [26]. In one series of 40 endometrial cancer cases in women less than 45 years old, 39 were premenopausal and presented with abnormal bleeding. The 40th woman was postmenopausal and also presented with bleeding. Thus, in this series, which was limited to younger women, no cases of endometrial cancer were diagnosed in the absence of abnormal bleeding [27].

In a series of 113 patients aged 25–69 who underwent SIS followed by hysteroscopic guided D+C because of persistent abnormal uterine bleeding, 39 polyps were noted in total (34% prevalence). Two of the 39 polyps were malignant (5% of polyps in women with irregular bleeding) [12]. A larger series of 1415

patients aged 23–85 referred for abnormal bleeding underwent D+C, revealing 126 polyps (8.9% prevalence). Two carcinomas were detected in 126 polyps (1.5% of polyps in women with abnormal bleeding) from hypertensive obese patients aged 68 and 75 years. Nine polyps demonstrated atypical hyperplasia, which is a premalignant change. In the 94 patients with benign polyps, D+C revealed carcinoma elsewhere in the uterus in 5. Thus, a total of 7/126 polyps (5.6% of all polyps) in women with abnormal bleeding were either carcinomatous or were contained within uteri where carcinoma was present elsewhere [28]. A third series documented endometrial cancer in 2 of 42 polyps (4.8%) diagnosed by SIS in patients referred for abnormal bleeding [29], yet an earlier series at the same center demonstrated no carcinomas in 56 polyps obtained from 433 perimenopausal women with abnormal bleeding [11].

At least one study has reported the presence of carcinoma in a polyp diagnosed in the absence of irregular bleeding. In this series, 19 polyps were detected by SIS in women referred for a variety of non-bleeding complaints, and malignancy was noted in one, a 36 year old patient [29]. Finally, a case-control study from Sweden found that 20% of 254 women with endometrial cancer had endometrial polyps, whereas polyps were present in 10% of age-matched control women [30].

Endometrial polyps are a common finding in infertile patients

Taken together, it can be concluded that the majority of endometrial cancer cases occur in women who are menopausal, and that the less common instances of premenopausal endometrial cancer are almost always associated with abnormal bleeding. It is appropriate to have an increased index of suspicion for neoplastic changes in women with a history of unopposed estrogen and in women who have used tamoxifen in the past. The risk of occult endometrial cancer in an infertile, regularly cycling, premenopausal infertile woman with a polyp discovered by SIS is not 0%, but it is extremely low.

Given the relationship between unopposed estrogen and carcinoma, and endometrial polyps and carcinoma, it will be important to ascertain if endometrial polyps are more prevalent in women with infertility associated with polycystic ovary syndrome and anovulation.

Detection of polyps by SIS

SIS is a highly sensitive, well-tolerated, safe, rapid, and minimally invasive means of detecting endometrial polyps [31]. The sensitivity, specificity, positive predictive value and negative predictive value of SIS in detecting endometrial polyps approach those of hysteroscopy (the "gold standard") and exceed those of transvaginal ultrasound and hysterosalpingography [15]. On SIS, polyps can usually be distinguished from submucosal fibroids even though both are focal and intracavitary. Polyps are usually smooth, hyperechoic and homogeneous although they may also contain small cystic components. Their attachment to the endometrial lining does not disrupt the lining. They can be sessile or pedunculated. Fibroids on the other hand are hypoechoic with a texture similar to myometrium. Shadowing can be seen. Overlying echogenic endometrium can often be imaged on SIS, defining the sub-endometrial location of the fibroid [32,33].

Conclusions

Endometrial polyps are a frequent finding in infertile patients. Hysteroscopic polypectomy is often recommended as a therapy for infertility. Little is known about the true prevalence of polyps in infertile patients, whether they are more prevalent in certain age groups, or whether there is a prevalence difference in infertile women depending on the etiology of the infertility. Do fertility drugs encourage polyp formation? Is the prevalence of polyps in infertile women higher than in the non-infertile population? All of these are important questions that must be answered in order to adequately design future randomized controlled trials to test the efficacy of and need for surgical intervention.

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