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No evidence to support the concept that endometrial polyps impair fertility in the majority of cases

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Summary

Purpose: To perform an updated literature search to determine whether hysteroscopic polypectomy helps to improve chance of pregnancy in infertile couples or reduce the risk of miscarriage. *Materials and Methods:* The authors conducted a personal review of the literature since 2009 (the last time such a search on the subject of polypectomy for infertility and miscarriage was performed by one of the authors). *Results:* No new studies were identified except a recent (2014) Cochrane Collaboration review from Polanski *et al.* was found. These authors had the same objective as we had in our previous publication in which an alleged randomized prospective trial (RCT) suggested that hysteroscopic polypectomy improved pregnancy rates following intrauterine insemination (IUI) *vs*. controls; however they included pregnancies obtained within three months after the procedure but before the four-month study period of IUI. Other flaws of the Perez-Medina study of 2005, that are even more significant, were pointed out by Polanski *et al. Conclusions:* Though no new studies shedding more insight whether the presence of endometrial polyps can impair fertility potential have been found, more flaws in design and conclusions of the one alleged RCT trail by Perez-Medina have been determined by a Cochrane review leading to the conclusion that there is not one properly designed and conducted RCT that supports hysteroscopic polypectomy to correct infertility in asymptomatic women. Though the possibility exists that irritating the endometrium by polypectomy can promote an inflammatory type endometrium, and thus improve embryo implantation and trophoblast invasion, other less invasive, less risky, less costly procedures can be performed, e.g., a single one swipe endometrial biopsy (now referred to as an endometrial scratch).

Key words: Endometrial polyp; Hysteroscopy; Endometrial inflammation; Endometrial irritation.

One of the standard tests for evaluating infertility is to perform a hysterosalpingogram (HSG). This HSG cannot only determine tubal patency but can detect uterine abnormalities including, but not limited to, endometrial polyps. Many infertility specialists will proceed with either a saline infusion sonography (SIS) or a hysteroscopy (especially if an office model is available), despite a normal endometrial cavity by HSG because these latter two tests may be better to detect endometrial polyps.

Physicians determine their own treatment strategies in many ways. Some physicians are only impressed with evidence-based medicine, and some even insist that only prospective randomized controlled trials (RCT) will dictate treatment policy, but what happens if there are no RCTs? A recent Cochrane collaboration meta-analysis could not find one properly performed RCT concerning the expectant management for endometrial polyps in subfertile women [1]. Nevertheless, in lieu of RCTs, many physicians will be guided by experts in the field. Thus for endometrial polyps, suggestions by expert hysteroscopic surgeons may greatly influence the treating physician, especially if editorials or reviews are in well-respected peer reviewed journals. A review by a world renowned pelvic surgeon, e.g., Victor Gomel, in one of the top infertility journals, Fertility and Sterility, would certainly provide a great influence to physicians practicing infertility. Indeed, in a 2008 review by Taylor and Gomel published, in Fertility and Sterility entitled "The uterus and fertility", they state that uterine polyps can cause infertility and recommended polypectomy (though they admitted that the mechanism was poorly understood [2]. Endometrial polyps are composed of tissues with irregular proliferative glands and stroma, thought to have progesterone receptor abnormalities. They are basically an overgrowth of vascular tissue originating from the spiral artery. Their etiology is poorly understood.

There are abundant theories how endometrial polyps can interfere with achieving a pregnancy, though conclusive evidence to support the theory on each instance is lacking. One of the earliest theories was that polyps interfered with responsiveness to the cyclical changes in estradiol and progesterone [3]. Others proposed that they simply created a mechanical barrier for sperm reaching the fallopian tubes, or mechanically blocked embryo implantation [4]. One theory was that polyps caused an increased production of gly-

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codelin which may inhibit natural killer cell function [5]. Natural killer cells may be important at the time of implantation to allow adequate depth of trophoblast invasion. Others suggested that they cause a decrease in cytokines needed for implantation, i.e., insulin-like growth factor binding protein–1, osteopontin, or tumor necrosis factor–alpha [6].

There had been several retrospective studies that failed to find a association of polyps and achieving a successful pregnancy. Mastromimas *et al.*, concluded that polyps < 2 cm diameter do not require removal before IVF since they do not seem to affect pregnancy outcome [7]. Similarly other retrospective studies found no association of the presence of endometrial polyps and pregnancy rates in IVF cycles [8-10].

In the modern era, changes in the philosophy of medical education have evolved so that there is less credence given to practicing in a certain way just because their mentor practiced that way, and possibly state that "in my experience this procedure, i.e., polypectomy, improves fecundity". The new student demands statistics. "Evidence-based medicine" has become the gold standard for many physicians.

A "prospective randomized study" showing that hysteroscopic polypectomy improves pregnancy rates in subsequent intrauterine insemination (IUI) cycles would influence many infertility specialists more than retrospective studies [11]. One study showed that women having polyps removed had 64 pregnancies out of 101 (63.3%) *vs*. 29 of 103 (28.2%) for controls [11]. Thus, on the surface, this study seems to strongly suggest the importance of polypectomy. However, there may be other interpretations as to the reason why the polypectomy group seemed to fare better than controls. The IUI was delayed three months and then four IUI cycles were evaluated. However, the authors included the three cycles while awaiting to start "the study" in interpreting pregnancy rates. Interestingly 42 of the 64 pregnancies in the polypectomy group conceived in the three cycles prior to starting IUI, whereas none of the controls conceived during that time [11]. Thus, if one eliminates the first three cycles, the pregnancy rate during the four IUI cycles was 37.2% for polypectomy *vs*. 28.2% for controls (which is no longer statistically significant). One may question why should these first three cycles not be included? In 2000 a study was published evaluating connexin-43 protein and gene expression throughout the menstrual cycle in the human endometrium [12]. The samples were obtained by endometrial biopsy [12]. These women may have volunteered in exchange for some financial considerations in a subsequent IVF cycle [12]. Though it was not the original intention of the study, the authors realized that the women who participated in the connexin-43 protein study had twice the pregnancy rates compared to other women having IVF who did not have a biopsy [13]. Thus it was concluded that local injury of the endometrium was responsible for this increase in pregnancy rates [13]. This was confirmed by other subsequent studies [14, 15]. There is evidence that the injury derived inflammation of the uterus provides a focus for uterine dendritic cell (DC) accumulation. The DC's produce essential cytokines and other molecules, e.g., chemokines, which attracts the embryos to attach and then implant into the endometrium and subsequently sufficient depth for adequate trophoblast invasion [16]. The aforementioned Cochrane collaboration review, i.e., meta-analysis, was performed to try to evaluate surgical intervention *vs*. expectant management for endometrial polyps in subfertile women [1]. The intention was to select only randomized controlled studies. The review was published in 2014 so there would be a new search since the RCT published by Perez-Medina in 2005 [11]. However, the Perez-Medina study was the only RCT that was found [1]. Unfortunately the selection criteria did not allow even this study to be included. The reason for rejection was that the authors could not extract a single set of results they could not resolve the internal inconsistencies reported. The Kaplan-Meier survival analysis curves (Figure 1 of the paper) showed higher survival rate in the treatment group, but the authors of the Cochrane collaboration review state their interpretation of the same figure suggested to them a lower pregnancy rate in the treatment group than the control group. Other inconsistencies were found by Polanski *et al.* but attempts to phone, e-mail, and post to contact the authors to resolve these queries were unsuccessful [1]. Thus, they decided to exclude the Perez-Medina study which left them with no RCTs to report. Thus, for those who require an RCT as evidence-based medicine to allow them to decide to perform a polypectomy or not, will not have an RCT to rely upon. In contrast, a Cochrane review of endometrial injury in women undergoing assisted reproductive techniques showed overwhelming improved pregnancy outcome based on RCTs [17]. Multiple studies qualified for inclusion in this report [17]. The point is that even though there does not appear to be any convincing evidence that removal of endometrial polyps improve fecundity (and several retrospective studies suggesting no benefit), any subsequent RCT evaluating effect of polypectomy on subsequent fecundity needs to exclude the possible confounding effect of endometrial injury.

Authors' personal opinion

An endometrial biopsy is a much less risky and much less expensive procedure compared to hysteroscopic polypectomy. An RCT should evaluate pregnancies occurring immediately after the procedure in both the treatment and control group without a delay in initiating treatment, e.g., IUI. Furthermore, the control group should not be an expectant group, but one receiving an endometrial biopsy in the preceding cycle to exclude the confounding variable ef-

fect of endometrial injury.

Certainly based on the lack of evidence that the presence of a small polyp < 1.5cm, or maybe even 2 cm, will impair the chance of conceiving or completing a pregnancy, there is no justification for a policy that we have witnessed when consulting patients with reproductive failure who have previously been treated by other infertility specialists, to subject a patient to an in-office hysteroscopy, or even performed in surgical centers (especially if the given physician has part ownership), in women having had recent previous HSGs that were normal. The alleged reason given to these patients is that whereas the HSG is good for determining tubal patency, often times it may miss endometrial polyps or adhesions that can be detected by hysteroscopy. Though not a subject for this editorial, there are no data supporting the importance of removing mild endometrial adhesions that are not impairing menstruation. In fact, there are some data that hysteroscopic resection of adhesions could lead to potential decreased fecundity based on adversely effecting endometrial thickness [18]. Thus, the purpose of writing this editorial is to make the practicing gynecologist and the practicing infertility specialist, rethink performing extra uncomfortable, expensive, and somewhat risky procedures on patients, e.g., hysteroscopies, without evidence of their benefit. There are no data supporting performing a hysteroscopic evaluation in a woman with a normal HSG and normal cavity by routine transvaginal sonography. One could question even the wisdom of polypectomy when a small polyp is seen on transvaginal sonography or HSG. Fortunately, we are not aware of any surgical complications in our practice from removing these polyps. However, the policy has had some negative effects for the patients. Some patients who have started controlled ovarian hyperstimulation for IVF have been told to stop stimulation and set up a consult for polypectomy, when one has been fortuitously seen on sonographic monitoring. Thus, they may have spent and wasted money on expensive gonadotropins and wasted the time away from work for sonographic and hormonal monitoring that has occurred prior to detecting the polypectomy. Sometimes the patient has been advised to proceed with the oocyte retrieval but freeze all the embryos, and defer the transfer until a polypectomy can be performed. This not only adds extra expense, but if the patient fails to conceive, the couple may question whether in some instances a couple's embryos are harmed by the cryopreservation, and maybe they may have conceived had a fresh transfer been performed. Thus, they may question whether a mistake was made by not performing a SIS first, and thus may request financial compensation for the "doctor error". These are not merely theoretical concerns, but have happened in our own practice, despite the knowledge that are our own retrospective matched controlled study failed to find any improved fertility following polypectomy [10].

We submitted our manuscripts over five years ago and I have not reviewed the subject since that time. So with the training of a new fellow, I thought we should look to see if there have been any new studies to favor polypectomy or not. Our own computer search failed to find any new studies, but we did find the aforementioned Cochrane review [1]. Jayaprakasan *et al.*, also found that there have not been any more RCTs on the subject since the Perez-Medina publication [1,11]. We had accepted the data from the Perez-Medina study as fact, but questioned the mechanism of improved pregnancy outcome from the endometrial injury *vs*. polypectomy (and the former would require a two-minute innocuous office procedure). However, this Cochrane review probed the Perez-Medina study much further than we did and found inconsistencies in the data [1]. The failure of these authors to respond to queries concerning these inconsistencies should exclude from the gynecologist's minds that despite the controversy, there is at least one RCT that supports polypectomy. Thus, the conclusion that we reached, is that there are no data supporting the conclusion that polypectomy improves fecundity in infertile women other than possibly by irritating the endometrium. Endometrial irritation can be performed by simply an endometrial scratch, which is far less invasive, does not require anesthesia, and is far less costly.

Often times the generalist is the main family physician for women and the ones whose opinion the women most respect. Thus, it may happen that if a gynecologist has performed an HSG which was normal, but an infertility specialist to where the patient was subsequently referred has suggested a hysteroscopy to look for subtle polyps or hysteroscopy to remove a small polyp, and the patient re-consults her gynecologist for their opinion as to the wisdom of performing the procedure, the gynecologist can at least make the patient aware that there are no data supporting the need for this procedure. The patient can then make up her own mind as to whether to proceed with hysteroscopy or not.

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