Published in final edited form as:

Fertil Steril. 2011 June 30; 95(8): 2690–2692. doi:10.1016/j.fertnstert.2010.12.034.

ENDOMETRIAL POLYPS AFFECT UTERINE RECEPTIVITY

Beth W. Rackow, MD, Elisa Jorgensen, BS, and Hugh S. Taylor, MD

Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine

Narrative abstract

This case-control study evaluated the effect of hysteroscopically identified endometrial polyps on endometrium using *HOXA10* and *HOXA11*, known molecular markers of endometrial receptivity. Uteri with endometrial polyps demonstrated a marked decrease in *HOXA10* and *HOXA11* mRNA levels that may impair implantation; these findings suggest a molecular mechanism to support clinical findings of diminished pregnancy rates in women with endometrial polyps.

Keywords

endometrial polyps; infertility; endometrial receptivity; *HOX* genes

Endometrial polyps are localized hyperplastic overgrowths of endometrium that contain both endometrial glands and stroma. The large majority of these lesions are benign. Polyps have a variable presentation; they can occur as individual or multiple lesions, range in size from millimeters to centimeters, and can be sessile or pedunculated. Although endometrial polyps may be identified during evaluation of abnormal bleeding, many polyps are asymptomatic and only discovered during the infertility evaluation. Up to 25% of women with unexplained infertility have endometrial polyps on hysteroscopy (1–3). However, their effect on endometrial receptivity and fertility is unclear.

Established markers of endometrial receptivity, *HOXA10* and *HOXA11*, were utilized to investigate the effect of endometrial polyps on endometrium. *HOXA10/Hoxa10* (human/mouse) is a homeobox-containing transcription factor that is essential for embryonic uterine development, essential for proper adult endometrial development during each menstrual cycle, and necessary for endometrial receptivity (4–11). Targeted mutation of *Hoxa10* produces mice that experience implantation failure, likely the sequela of absent *Hoxa10* during embryonic uterine development and the direct effect of absent *Hoxa10* during cyclic adult endometrial development (12). Furthermore, decreased *Hoxa10* expression correlates with diminished implantation, which suggests that an altered level of *Hoxa10* regulates the degree of endometrial receptivity (5). Similarly, a targeted mutation of *Hoxa11* results in uterine factor infertility and poor endometrial glandular development (13,14). *Hoxa11* heterozygotes have lower levels of *Hoxa11* expression and diminished implantation rates (14).

Corresponding author: Beth W. Rackow, MD, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, P.O. Box 208063, New Haven, CT 06520-8063, (203) 737-5619, fax (203) 785-7134, beth.rackow@yale.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

In humans, *HOXA10* and *HOXA11* are expressed in proliferative phase endometrial glands and stroma, and expression of these genes is markedly upregulated in the midsecretory glands at the time of implantation (8,15–18). Both estrogen and progesterone upregulate *HOXA10* and *HOXA11* expression (8,17). The pattern of *HOXA10* and *HOXA11* expression suggests a critical role in the implantation process. Furthermore, downstream target genes involved in implantation regulated by *HOXA10* include β_3 integrin, *EMX2*, and *IGFBP-1*, and *KLF9* (19–22). Defective *HOXA10* expression has been demonstrated in conditions associated with implantation such as endometriosis, polycystic ovarian syndrome (PCOS), hydrosalpinges and submucosal myomas (9,15,23–25). This study investigated the effect of endometrial polyps on endometrium by evaluating established markers of endometrial receptivity, *HOXA10* and *HOXA11*.

This case-control study included 30 subjects, 21 with endometrial polyps and 9 with a normal uterine cavity without polyps. Subjects were identified at the time of hysteroscopy for evaluation of the endometrial cavity prior to infertility treatment. One-half of the subjects had a known endometrial abnormality identified during a sonohysterogram, and nine subjects were considered controls after finding a normal uterine cavity. At the time of surgery, the following data were obtained: age, obstetric and gynecologic history, medical conditions, medications, surgical history, last menstrual period, preoperative and postoperative diagnoses, and operative findings. Subjects had not used hormonal medications for at least 3 months prior to surgery, and had regular menstrual periods. Subjects did not have any confounding medical conditions known to affect endometrial receptivity such as endometriosis, PCOS, hydrosalpinges or submucosal myomas. This study was approved by the Yale University School of Medicine Human Investigation Committee.

All subjects underwent hysteroscopy in the proliferative phase of the menstrual cycle. When an endometrial polyp was present, it was excised under hysteroscopic guidance. Endometrial curettage was performed in all procedures, and the endometrial specimen was divided for pathology evaluation and laboratory investigation.

At surgery, each endometrial tissue sample was stored in 1 ml of RNeasy lysis solution (Qiagen, Valencia, CA) at -80°C until RNA isolation. RNA was processed as previously described (25). Messenger RNA levels were analyzed by quantitative real-time RT-PCR using the Bio-Rad iCycler iQ system (Bio-Rad Laboratories, Hercules, CA). For each sample, 500ng of total RNA was reverse transcribed using an iScript cDNA Synthesis Kit (Bio-Rad Laboratories, Hercules, CA). Real-time RT-PCR was performed using a MyiQ Single Color Real-Time PCR Detection System and iQ SYBR Green Supermix (both, Bio-Rad). The sequences of all primers and the real time RT-PCR reaction conditions have been previously published (25). Melting curve data were collected and analyzed. Each assay was run in duplicate with each set of primers, and samples without mRNA were included as negative controls. *HOXA10* and *HOXA11* gene expression was normalized to the expression of β -actin for each sample. Relative mRNA expression levels for each gene were calculated using the $2^{-\Delta\Delta\text{CT}}$ method (26). Differences in endometrial *HOXA10* and *HOXA11* expression between the polyp and control groups were determined using Student's t-test; $p < 0.05$ was considered statistically significant.

Mean subject age was 33.6 years (range 22–41 years). There was no difference in mean age between the two groups. Twenty-one subjects had endometrial polyps, and polyp size ranged from 3–20mm. The number of polyps ranged from 1–4, and 6 of 21 subjects (28.6%) had more than one polyp.

All samples underwent histological evaluation; benign endometrial polyps were identified, and curettage samples revealed normal proliferative endometrium. Endometrium from subjects with and without polyps was evaluated for *HOXA10* and *HOXA11* mRNA expression.

Compared to controls, endometrial *HOXA10* mRNA expression (normalized to β -Actin expression) was significantly decreased in uterine cavities with polyps (0.334 $\times$ control; $p=0.016$; Figure 1). Similar findings were seen for endometrial *HOXA11* mRNA expression in the presence of a polyp compared to controls (0.183 $\times$ control; $p=0.03$; Figure 1). When polyp samples were compared based on polyp size [<8 mm polyps ($n=15$) versus ≥ 8 mm polyps ($n=6$)], there were no differences in *HOXA10* ($p=0.354$) or *HOXA11* ($p=0.11$) expression. Similarly, the presence of single ($n=15$) versus multiple ($n=6$) polyps did not affect *HOXA10* ($p=0.092$) or *HOXA11* ($p=0.795$) expression.

The effect of asymptomatic endometrial polyps on infertility is unclear. However, it is plausible that polyps can cause infertility due to mechanical interference with sperm and embryo transport, impairment of embryo implantation or altered endometrial receptivity. Furthermore, the size, number or location of polyps may influence any effect on reproductive outcomes.

Several studies have investigated the effect of endometrial polyps on pregnancy rates for infertile women who underwent intrauterine insemination (IUI) or in vitro fertilization (IVF), or who conceived spontaneously, and disparate results were obtained. One prospective randomized trial ($n=215$) identified significant improvement in pregnancy rates after hysteroscopic polypectomy and up to four cycles of controlled ovarian hyperstimulation with gonadotropins plus IUI (63% vs. 28%, $p<0.001$) (27). In this study, all polyps were visualized hysteroscopically, and the study group underwent hysteroscopic polypectomy and the control group underwent hysteroscopic biopsy of the polyp. Additionally, several nonrandomized studies of women with unexplained infertility and polyps demonstrated an improvement in spontaneous pregnancy rates after undergoing hysteroscopic polypectomy (3,28,29). In contrast, several studies of women undergoing IVF have not demonstrated impairment of pregnancy rates in the presence of polyps <2 cm in size (30,31), although one study (31) noted an increased miscarriage rate in the polyp group and recommends embryo cryopreservation if a polyp is identified. These IVF studies included 15 and 49 subjects, respectively, with polyps who underwent IVF, and may have been underpowered to detect a difference in pregnancy rates. Hence, a better understanding of the effect of polyps on infertility and pregnancy is warranted.

The effect of polyps on the endometrium was evaluated using *HOXA10* and *HOXA11*, established molecular markers of endometrial receptivity. Significantly lower *HOXA10* and *HOXA11* expression was identified in endometrium from uteri with polyps compared to controls, suggestive of impaired endometrial receptivity in uteri with polyps. The presence of a polyp may alter *HOX* gene expression throughout the endometrium, and changes in endometrial signaling pathways lead to impaired endometrial receptivity. These findings provide molecular data to support some clinical findings that pregnancy rates improve after hysteroscopic polypectomy. Furthermore, these findings mirror our findings of impaired endometrial receptivity in uteri with submucosal myomas (25). This study did not have the power to assess differences in these markers based on the number of polyps or polyp size, and future studies should investigate these questions. It is not known if there is a threshold size above which a polyp causes a significant clinical effect.

Research on uterine myomas and infertility may help guide recommendations for the management of polyps in infertile women. It has been established that submucosal myomas

negatively impact fertility and pregnancy rates, and surgical removal of submucosal myomas leads to improved pregnancy rates (32). Furthermore, when a submucosal myoma is present, endometrial receptivity is globally impaired throughout the uterine cavity (25), and this finding may explain the reproductive dysfunction observed with submucosal myomas. Here we show that endometrial polyps have an effect on markers of endometrial receptivity that is similar to the effect seen with fibroids; these two conditions likely both affect endometrial receptivity through similar molecular mechanisms.

Our finding of impaired endometrial receptivity in uteri with one or more endometrial polyps supports the results from the one randomized trial demonstrating the negative effect of polyps on fertility (27). Detailed evaluation of the uterine cavity is essential in infertile women, and if an endometrial polyp is identified, hysteroscopic polypectomy prior to infertility treatment is reasonable and recommended as this intervention may improve fertility. Further studies are warranted to evaluate if markers of endometrial receptivity normalize after removal of the polyp.

Acknowledgments

Support: NIH HD036887 and HD052668

References

1. de Sa Rosa e de Silva AC, Rosa e Silva JC, Candido dos Reis FJ, Nogueira AA, Ferriani RA. Routine office hysteroscopy in the investigation of infertile couples before assisted reproduction. *J Reprod Med.* 2005; 50:501–6. [PubMed: 16130847]
2. Kim MR, Kim YA, Jo MY, Hwang KJ, Ryu HS. High frequency of endometrial polyps in endometriosis. *J Am Assoc Gynecol Laparosc.* 2003; 10:46–8. [PubMed: 12554993]
3. Shokeir TA, Shalan HM, El-Shafei MM. Significance of endometrial polyps detected hysteroscopically in eumenorrheic infertile women. *J Obstet Gynaecol Res.* 2004; 30:84–9. [PubMed: 15009608]
4. Bagot CN, Kliman HJ, Taylor HS. Maternal Hoxa10 is required for pinopod formation in the development of mouse uterine receptivity to embryo implantation. *Dev Dyn.* 2001; 222:538–44. [PubMed: 11747087]
5. Bagot CN, Troy PJ, Taylor HS. Alteration of maternal Hoxa10 expression by in vivo gene transfection affects implantation. *Gene Ther.* 2000; 7:1378–84. [PubMed: 10981664]
6. Block K, Kardana A, Igarashi P, Taylor HS. In utero diethylstilbestrol (DES) exposure alters Hox gene expression in the developing müllerian system. *FASEB J.* 2000; 14:1101–8. [PubMed: 10834931]
7. Taylor HS. The role of HOX genes in human implantation. *Hum Reprod Update.* 2000; 6:75–9. [PubMed: 10711832]
8. Taylor HS, Arici A, Olive D, Igarashi P. HOXA10 is expressed in response to sex steroids at the time of implantation in the human endometrium. *J Clin Invest.* 1998; 101:1379–84. [PubMed: 9525980]
9. Taylor HS, Bagot C, Kardana A, Olive D, Arici A. HOX gene expression is altered in the endometrium of women with endometriosis. *Hum Reprod.* 1999; 14:1328–31. [PubMed: 10325287]
10. Taylor HS, Daftary GS, Selam B. Endometrial HOXA10 expression after controlled ovarian hyperstimulation with recombinant follicle-stimulating hormone. *Fertil Steril.* 2003; 80:839–43. [PubMed: 14505762]
11. Taylor HS, Vanden Heuvel GB, Igarashi P. A conserved Hox axis in the mouse and human female reproductive system: late establishment and persistent adult expression of the Hoxa cluster genes. *Biol Reprod.* 1997; 57:1338–45. [PubMed: 9408238]
12. Satokata I, Benson G, Maas R. Sexually dimorphic sterility phenotypes in Hoxa10-deficient mice. *Nature.* 1995; 374:460–3. [PubMed: 7700356]

13. Gendron RL, Paradis H, Hsieh-Li HM, Lee DW, Potter SS, Markoff E. Abnormal uterine stromal and glandular function associated with maternal reproductive defects in Hoxa-11 null mice. *Biol Reprod.* 1997; 56:1097–105. [PubMed: 9160706]
14. Hsieh-Li HM, Witte DP, Weinstein M, Branford W, Li H, Small K, et al. Hoxa 11 structure, extensive antisense transcription, and function in male and female fertility. *Development.* 1995; 121:1373–85. [PubMed: 7789268]
15. Gui Y, Zhang J, Yuan L, Lessey BA. Regulation of HOXA-10 and its expression in normal and abnormal endometrium. *Mol Hum Reprod.* 1999; 5:866–73. [PubMed: 10460226]
16. Sarno JL, Kliman HJ, Taylor HS. HOXA10, Pbx2, and Meis1 protein expression in the human endometrium: formation of multimeric complexes on HOXA10 target genes. *J Clin Endocrinol Metab.* 2005; 90:522–8. [PubMed: 15494461]
17. Taylor HS, Igarashi P, Olive DL, Arici A. Sex steroids mediate HOXA11 expression in the human peri-implantation endometrium. *J Clin Endocrinol Metab.* 1999; 84:1129–35. [PubMed: 10084606]
18. Wang LF, Luo HZ, Zhu ZM, Wang JD. Expression of HOXA11 gene in human endometrium. *Am J Obstet Gynecol.* 2004; 191:767–72. [PubMed: 15467538]
19. Daftary GS, Troy PJ, Bagot CN, Young SL, Taylor HS. Direct regulation of beta3-integrin subunit gene expression by HOXA10 in endometrial cells. *Mol Endocrinol.* 2002; 16:571–9. [PubMed: 11875117]
20. Du H, Sarno J, Taylor HS. HOXA10 inhibits Kruppel-like factor 9 expression in the human endometrial epithelium. *Biol Reprod.* 2010; 83:205–11. [PubMed: 20463357]
21. Kim JJ, Buzzio OL, Li S, Lu Z. Role of FOXO1A in the regulation of insulin-like growth factor-binding protein-1 in human endometrial cells: interaction with progesterone receptor. *Biol Reprod.* 2005; 73:833–9. [PubMed: 15987820]
22. Troy PJ, Daftary GS, Bagot CN, Taylor HS. Transcriptional repression of peri-implantation EMX2 expression in mammalian reproduction by HOXA10. *Mol Cell Biol.* 2003; 23:1–13. [PubMed: 12482956]
23. Cermik D, Selam B, Taylor HS. Regulation of HOXA-10 expression by testosterone in vitro and in the endometrium of patients with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2003; 88:238–43. [PubMed: 12519859]
24. Daftary GS, Taylor HS. Hydrosalpinx fluid diminishes endometrial cell HOXA10 expression. *Fertil Steril.* 2002; 78:577–80. [PubMed: 12215336]
25. Rackow BW, Taylor HS. Submucosal uterine leiomyomas have a global effect on molecular determinants of endometrial receptivity. *Fertil Steril.* 2010; 93:2027–34. [PubMed: 18555231]
26. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2⁻(Delta Delta C(T)) Method. *Methods.* 2001; 25:402–8. [PubMed: 11846609]
27. Perez-Medina T, Bajo-Arenas J, Salazar F, Redondo T, Sanfrutos L, Alvarez P, et al. Endometrial polyps and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. *Hum Reprod.* 2005; 20:1632–5. [PubMed: 15760959]
28. Spiewankiewicz B, Stelmachow J, Sawicki W, Cendrowski K, Wypych P, Swiderska K. The effectiveness of hysteroscopic polypectomy in cases of female infertility. *Clin Exp Obstet Gynecol.* 2003; 30:23–5. [PubMed: 12731738]
29. Varasteh NN, Neuwirth RS, Levin B, Keltz MD. Pregnancy rates after hysteroscopic polypectomy and myomectomy in infertile women. *Obstet Gynecol.* 1999; 94:168–71. [PubMed: 10432121]
30. Isikoglu M, Berkkanoglu M, Senturk Z, Coetzee K, Ozgur K. Endometrial polyps smaller than 1.5 cm do not affect ICSI outcome. *Reprod Biomed Online.* 2006; 12:199–204. [PubMed: 16478585]
31. Lass A, Williams G, Abusheikha N, Brinsden P. The effect of endometrial polyps on outcomes of in vitro fertilization (IVF) cycles. *J Assist Reprod Genet.* 1999; 16:410–5. [PubMed: 10478319]
32. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. *Fertil Steril.* 2009; 91:1215–23. [PubMed: 18339376]

Figure 1.
(A) Endometrial *HOXA10* gene expression in control and polyp groups; (B) Endometrial *HOXA11* gene expression in control and polyp groups.