



Published in final edited form as:

Semin Reprod Med. 2010 January ; 28(1): 69–74. doi:10.1055/s-0029-1242996.

Molecular Mechanisms of Treatment Resistance in Endometriosis: The Role of Progesterone–Hox Gene Interactions

Hakan Cakmak, M.D.¹ and Hugh S. Taylor, M.D.¹

Serdar E. Bulun, M.D.

Progesterone Resistance and Endometrial Disease

¹Department of Obstetrics, Gynecology & Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut.

Abstract

HOX genes, encoding homeodomain transcription factors, are dynamically expressed in endometrium, where they are necessary for endometrial growth, differentiation, and implantation. In human endometrium, the expression of HOXA10 and HOXA11 is driven by sex steroids, with peak expression occurring at time of implantation in response to rising progesterone levels. However, the maximal HOXA10 and HOXA11 expression fails to occur in women with endometriosis. In endometriosis, altered progesterone receptor expression or diminished activity may lead to attenuated or dysregulated progesterone response and decreased expression of progesterone-responsive genes including HOX genes in the eutopic endometrium. In turn, other mediators of endometrial receptivity that are regulated by HOX genes, such as pinopodes, $\alpha\beta 3$ integrin, and IGFBP-1, are downregulated in endometriosis. HOXA10 hypermethylation has recently been demonstrated to silence HOXA10 gene expression and account for decreased HOXA10 in the endometrium of women with endometriosis. Silencing of progesterone target genes by methylation is an epigenetic mechanism that mediates progesterone resistance. The relatively permanent nature of methylation may explain the widespread failure of treatments for endometriosis-related infertility.

Keywords

HOX genes; implantation; endometrium; endometriosis

Homeobox (Hox) genes were originally discovered in the fruit fly *Drosophila*, where they function through a conserved homeodomain as transcriptional regulators to control embryonic morphogenesis.¹ Since then, >1000 homeodomain proteins have been identified in several species. In nonprimates (Hox genes) and primates (HOX genes), 39 Hox genes have been identified as homologs of the original *Drosophila* complex. They are organized into four Hox loci, each localized on a different chromosome (HOX A at 7p15.3, HOX B at 17p21.3, HOX C at 12q13.3, and HOX D at 2q31) and containing from 9 to 11 genes.² On the basis of sequence similarity and position on the locus, corresponding genes in the four clusters can be aligned with each other into 13 paralogous groups.³ During mammalian

development, Hox gene expression controls the identity of various regions along the body axis according to the rules of temporal and spatial colinearity, with 3' Hox genes expressed early in development and controlling anterior regions, followed by progressively more 5' genes expressed later and controlling more posterior regions.⁴ Individual genes of the HOXA cluster assign distinct identity to each segment of the paramesonephric duct, resulting in the development of the fallopian tube (hoxa9), uterus (hoxa10), lower uterine segment and cervix (hoxa11), and upper vagina (hoxa13).⁵ Furthermore, the lack of appropriate HOX gene expression leads to developmental anomalies. For example, in utero exposure to diethylstilbestrol, a well-known teratogen, induces a posterior shift of murine HOX gene expression, resulting in the homeotic anterior transformations of the reproductive tract that mimic the abnormalities noted in humans.⁶

Hox genes were originally considered to be expressed only during the embryonic development. However, the persistent expression of hox genes has been noted in the reproductive tract.^{5,7} In this review, we summarize the regulation and roles of hox genes in response to sex steroids in endometrium and endometriosis.

REGULATION OF HOX GENES BY SEX STEROIDS IN ENDOMETRIUM

During each reproductive cycle, endometrial epithelial and stromal cells display a well-defined pattern of functional differentiation that is necessary for successful pregnancy under the cyclic influence of estrogen and progesterone. Initial proliferation is followed by differentiation leading to a receptive state for embryo implantation. In the absence of implantation, however, apoptosis and degeneration of the endometrium is observed. The great body of evidence suggests that HOX genes are essential for endometrial growth, differentiation, and receptivity by mediating some functions of the sex steroids during each reproductive cycle.

HOXA10 and HOXA11 demonstrate a temporal pattern of expression in endometrial cells through the reproductive cycle.^{8,9} HOXA10 and HOXA11 mRNA are both expressed in human endometrial epithelial and stromal cells, and their expression is significantly higher in the mid- and late secretory phases, coinciding with time of embryo implantation and high levels of estrogen and progesterone.⁸⁻¹⁰ Moreover, in the case of successful implantation, the decidua of the early pregnancy continues to express high levels of HOXA10 and HOXA11 mRNA.^{8,9}

Menstrual cyclicity is regulated by timed expression of estrogen and progesterone, which act both independently and in concert to upregulate HOXA10 and HOXA11 expression in endometrium. In endometrial stromal cells, 17 β -estradiol significantly increased HOXA10 mRNA expression in a dose-dependent manner. Similar effect of 17 β -estradiol on HOXA10 mRNA expression was also observed in Ishikawa cells, a well-differentiated endometrial adenocarcinoma cell line, which is known to express the estrogen and progesterone receptors and serves as a model of endometrial epithelium.⁸ Likewise, HOXA10 mRNA levels were significantly increased in primary endometrial stromal cells treated with the progestin medroxyprogesterone acetate (MPA). This response to MPA was greater than to 17 β -estradiol, and combination treatment of 17 β -estradiol and MPA induced higher levels of HOXA10 mRNA expression compared with treatment with either hormone alone.⁸ However, progestational regulation of HOXA10 was blocked by RU-486, a specific progesterone receptor antagonist, in primary endometrial cells.^{9,11} A similar expression pattern of HOXA11 was also demonstrated in response to estrogen and progesterone in endometrial cells.⁹ Furthermore, these effects of estrogen and progesterone are mediated through their cognate receptors binding to the regulatory regions of the Hoxa10 or Hoxa11 genes.^{9,11-13}

ROLES OF HOX GENES IN ENDOMETRIUM

The pattern of HOX gene expression under the influence of estrogen and progesterone in endometrium suggests that HOX genes are necessary for implantation in humans. As transcription factors, they regulate other downstream target genes leading to proper development of the endometrium and receptivity to implantation. Both *hoxa10* and *hoxa11* are necessary for fertility in mice. Although *hoxa10* or *hoxa11* knockout mice produce a normal number of embryos and these embryos survive in a wild-type surrogate, wild-type embryos from the surrogate mice cannot implant in the *Hoxa10*- and *Hoxa11*-deficient mice, suggesting uterine factor infertility due to implantation defects.^{7,14,15} The importance of *Hoxa10* in implantation is further supported by experiments using antisense oligonucleotides to *Hoxa10* that were injected into the mouse uterus, and as a result, implantation rates decreased.¹⁶

Impaired endometrial receptivity is considered to be a major limiting factor for the establishment of pregnancy. In an attempt to develop a clinically relevant and reproducible evaluation of endometrial function, several molecular and morphological markers specific to the implantation window have been identified. Some of these markers were shown to be regulated by Hox genes including pinopodes, $\beta 3$ integrin, insulin-like growth factor-binding protein-1 (IGFBP-1), and prostaglandins.¹⁷

Pinopodes are cytoplasmic protrusions on the apical surface of the luminal epithelium that can be visualized by scanning electron microscopy, and the surfaces pinopodes may have receptors for adhesion molecules, which are essential for embryo implantation.¹⁸ Pinopodes are progesterone-dependent structures whose appearance coincides with the onset of implantation window.^{19,20} HOXA10 antisense treatment diminishes pinopode number, whereas an increase is observed when uterine HOXA10 expression is upregulated.²¹ Pinopode development may therefore represent a morphological feature of HOXA10-induced endometrial functional differentiation.

Integrins are a family of cell adhesion molecules that function in both cell–cell and cell–substratum adhesion. They promote cell attachment to proteins within the extracellular matrix and potentiate cell migration and invasion. Many members of the integrin family are expressed by the endometrium throughout the menstrual cycle. Among these, the expression of $\alpha v\beta 3$ integrin at apical surface of luminal endometrial epithelium is critical; it is expressed during the secretory phase of the menstrual cycle after cycle day 20, around the time of embryo implantation, and has a role in the initial embryo–endometrial interaction.^{22,23} Temporally, this period is associated with high levels of expression of progesterone and its target HOXA10. Moreover, HOXA10 has been shown to directly regulate the expression of $\beta 3$ integrin through a consensus Abd-B type HOX binding site located 5' of the $\beta 3$ integrin gene within its regulatory region.²⁴

IGFBP-1 was first characterized as a soluble protein modulating the bioavailability of IGF-I and IGF-II. Human decidualized endometrial stromal cells express IGFBP-1.²⁵ It has been hypothesized that a paracrine interaction at the maternal–fetal interface occurs between decidual IGFBP-1 and fetal trophoblast-expressed IGF-II that is necessary for embryo implantation.²⁶ In baboon and human endometrial stromal cells, HOXA10 interacts with the FOXO transcription factor FKHR, and together this heterodimer upregulates IGFBP-1 expression.^{27–29}

Prostaglandin(PG)E₂ and PGI₂ have been implicated in both endometrial decidualization and embryo implantation by regulating mitogenic and vasogenic processes.³⁰ PGE₂ activates a distinct set of cell-surface receptors (EP1 to 4), of which two subtypes, EP3 and EP4, are aberrantly expressed in the endometrial stromal cells in *Hoxa10* knockout mice.³¹

Endometrial stromal EP3 and EP4 expression is diminished in response to treatment with progesterone in the absence of *Hoxa10*, suggesting that *Hoxa10* specifically mediates progesterone regulation of EP3 and EP4.³¹

There are no documented human mutations in *HOXA10* or *HOXA11*. However, women with decreased expression of these two genes during the secretory phase have lower implantation rates as seen in endometriosis, polycystic ovarian syndrome, hydrosalpinx, and fibroids.^{32–35}

PROGESTERONE–HOX GENE INTERACTIONS IN ENDOMETRIOSIS

Endometriosis is defined by the presence of viable endometrial tissue outside the uterine cavity. The prevalence of endometriosis approaches 6 to 10% in the general reproductive-age female population and to 25 to 50% in women with infertility.³⁶ Moreover, among women with endometriosis, 30 to 50% are infertile.³⁷ There are multiple proposed mechanisms of subfertility in endometriosis, including altered folliculogenesis, impaired fertilization, defective implantation, and poor oocyte quality with decreased ability to implant.^{38–40}

Estrogen and progesterone are the master regulators of endometrial tissue, and they regulate expression of hundreds of genes during various phases of the menstrual cycle.⁴¹ Both endometriotic and endometrial tissues possess estrogen and progesterone receptors, and they respond to these sex steroids by apparently similar histological changes. However, an attenuated or dysregulated progesterone response at the molecular level is suggested in endometriosis, and interestingly, progestin-based treatment of this disorder is variably effective.^{42,43}

The effects of progesterone are mediated via intracellular progesterone receptors that are expressed from a single gene as two protein isoforms, progesterone receptor A (PR-A) and progesterone receptor B (PR-B).⁴⁴ PR-A is a 94-kDa protein, whereas PR-B is an ~114-kDa protein that contains additional 164 amino acids at its amino terminal.⁴⁵ In normal human endometrial epithelium, both PR-A and PR-B are increased by estrogen during the proliferative phase but are reduced during the secretory phase under the influence of rising serum progesterone levels.^{46,47} PR-A predominates throughout the cycle in the stromal cells, suggesting a function in progesterone-mediated stromal decidualization.⁴⁶ Generation of knockout mice with selective ablation of PR-A or PR-B has provided in vivo proof that only PR-A, but not PR-B, is necessary to elicit progesterone-dependent reproductive responses.^{48,49} PR-A knockout mice have defective implantation due to loss of progesterone-regulated expression of genes associated with uterine receptivity.⁴⁹ However, PR-B knockout mice are fertile and sustain a normal pregnancy, suggesting normal uterine responses to progesterone.⁴⁹

Alteration in the ratio of PR-A to PR-B was suggested as one of the possible mechanisms of progesterone resistance in endometriosis.⁵⁰ In murine endometriosis model, decreased PR-A mRNA and increased ratio of PR-B to PR-A mRNA and total PR protein expressions were detected in the eutopic endometrium compared with controls.⁵⁰ PR expression was also found to be similarly altered in the eutopic endometrium of baboons with induced endometriosis.⁵¹ Consistent with these animal models of endometriosis, a microarray-based study in women with moderate to severe endometriosis also reported increased total PR in women with endometriosis.⁵² This altered PR expression may lead to diminished PR response and decreased expression of progesterone-responsive genes in endometriosis.

Multiple gene expression profiles by microarray in endometrium of women with or without endometriosis showed that several progesterone target genes were dysregulated during the

window of implantation, leading to an inhospitable environment for implanting blastocyst.⁵²⁻⁵⁴ Two of the progesterone target genes that are dysregulated in endometriosis are Hox genes. As discussed earlier, the expression of both HOXA10 and HOXA11 rises dramatically during the implantation window and remains elevated throughout the rest of the luteal phase.^{8,9} However, the peak of HOXA10 and HOXA11 expressions fails to occur in women with endometriosis.³⁵ Similarly, in mice and baboons with induced endometriosis, HOXA expression was down-regulated in eutopic endometrium.^{29,50} Furthermore, the expression of various other mediators of endometrial receptivity that are also mediated by HOX genes, such as pinopodes, $\alpha\beta3$ integrin, and IGFBP-1, are found to be decreased in endometriosis.^{50,55-57} The expression of the Empty spiracles homolog 2 (Emx2/EMX2) gene, associated with defective implantation, is repressed by elevated levels of HOXA in normal endometrium during the window of implantation.⁵⁸ However, diminished HOXA10 expression in endometriosis derepresses EMX2 repression, which manifests as simultaneously elevated levels of endometrial EMX2 mRNA.⁵⁹ Consistent with the fact that high peri-implantation endometrial EMX2 levels are associated with a defective implantation phenotype in patients with endometriosis, there is a significant 40% decrease in the litter size of mice transfected with EMX2 cDNA in the peri-implantation period.⁶⁰

EPIGENETIC REGULATION OF HOX GENES IN ENDOMETRIOSIS

Epigenetics refers to heritable changes in DNA and chromatin that impact gene expression without changes in DNA sequence.⁶¹ The two basic epigenetic regulatory mechanisms are DNA methylation and histone modifications.⁶¹ DNA methylation refers to the covalent modification of postreplicative DNA, which adds a methyl group to the cytosine ring to form methyl cytosine.⁶² In mammals, this modification is found mainly in CpG dinucleotides in the context of cytosines followed by guanine, or the so-called CpG sites.⁶² When promoter CpG islands are methylated, the associated gene typically becomes silenced due to suppressed transcriptional activity.⁶² In humans, DNA methylation is a crucial epigenetic modification of the genome that plays an important role in the regulation of gene expression and genomic imprinting, cell differentiation, and regulation of many other cellular processes.^{61,62} Aberrant DNA methylation has been recognized as an important mechanism in tumorigenesis and multiple other diseases.^{63,64}

Recent animal and human studies have reported HOXA10 hypermethylation as one of the possible mechanisms by which HOXA10 levels are decreased in endometriosis.^{29,50,65} In both mouse and baboon endometriosis models, hypermethylation of the 5' promoter region of Hoxa10/HOXA10 and decreased expression of Hoxa10/HOXA10 genes were demonstrated in eutopic endometrium.^{29,50} In human, three CpG-rich fragments in HOXA10 gene were identified (one in the 50 upstream of exon 1, and two in the intronic region sandwiched by exons 1 and 2), and HOXA10 was hypermethylated in all fragments in the endometrium of women with endometriosis compared with controls.⁶⁵ Moreover, the genes coding for the enzymes that catalyze DNA methylation (i.e., DNA methyltransferase [DNMT] 1, 3A, and 3B) were overexpressed in the epithelial component of endometriotic implants compared with normal controls.⁶⁶ However, only DNMT3A was found to be upregulated in eutopic endometrium of women with endometriosis.⁶⁶

HOXA10 hypermethylation, a novel mechanism of HOX gene dysregulation, permanently silences HOXA10 gene expression in endometriosis. Given that HOX genes modulate some of the functions of progesterone, decreased HOXA10 expression due to hypermethylation may result in resistance to progesterone action in endometriotic tissues. This novel mechanism of progesterone resistance may also explain the medical treatment failures in endometriosis.

CONCLUSIONS

Hox genes are necessary for endometrial responsiveness to progesterone during decidualization and implantation. Resistance to progesterone can explain inhospitable implantation environment and medical treatment failures in endometriosis. Alterations in progesterone receptor expression and decreased HOX gene expression secondary to hypermethylation of its promoter region are the possible mechanisms of the progesterone resistance. Further, the permanent nature of hypermethylation may explain the resistance of endometriosis to other medical and surgical therapies as well. A gene therapy approach involving the manipulation of HOXA10 expression or by using DNA demethylation agents to restore methylation aberrations can potentially have a role in the future treatment of endometriosis.

Acknowledgments

Support was received from NIH grants U54 HD052668 and R01 HD036887.

REFERENCES

1. Gehring WJ, Hiromi Y. Homeotic genes and the homeobox. *Annu Rev Genet.* 1986; 20:147–173. [PubMed: 2880555]
2. Apiou F, Flagiello D, Cillo C, Malfoy B, Poupon MF, Dutrillaux B. Fine mapping of human HOX gene clusters. *Cytogenet Cell Genet.* 1996; 73(1-2):114–115. [PubMed: 8646877]
3. Scott MP. Vertebrate homeobox gene nomenclature. *Cell.* 1992; 71(4):551–553. [PubMed: 1358459]
4. Dekker EE, Kitson RP. 2-Keto-4-hydroxyglutarate aldolase: purification and characterization of the homogeneous enzyme from bovine kidney. *J Biol Chem.* 1992; 267(15):10507–10514. [PubMed: 1587831]
5. 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(6):1338–1345. [PubMed: 9408238]
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(9):1101–1108. [PubMed: 10834931]
7. Benson GV, Lim H, Paria BC, Satokata I, Dey SK, Maas RL. Mechanisms of reduced fertility in Hoxa-10 mutant mice: uterine homeosis and loss of maternal Hoxa-10 expression. *Development.* 1996; 122(9):2687–2696. [PubMed: 8787743]
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(7):1379–1384. [PubMed: 9525980]
9. 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(3):1129–1135. [PubMed: 10084606]
10. 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(5):1097–1105. [PubMed: 9160706]
11. Ma L, Benson GV, Lim H, Dey SK, Maas RL, Abdominal B. Abdominal B (AbdB) Hoxa genes: regulation in adult uterus by estrogen and progesterone and repression in müllerian duct by the synthetic estrogen diethylstilbestrol (DES). *Dev Biol.* 1998; 197(2):141–154. [PubMed: 9630742]
12. Akbas GE, Song J, Taylor HSA. A HOXA10 estrogen response element (ERE) is differentially regulated by 17 beta-estradiol and diethylstilbestrol (DES). *J Mol Biol.* 2004; 340(5):1013–1023. [PubMed: 15236964]

13. Martin R, Taylor MB, Krikun G, Lockwood C, Akbas GE, Taylor HS. Differential cell-specific modulation of HOXA10 by estrogen and specificity protein 1 response elements. *J Clin Endocrinol Metab.* 2007; 92(5):1920–1926. [PubMed: 17311863]
14. Hsieh-Li HM, Witte DP, Weinstein M, et al. Hoxa 11 structure, extensive antisense transcription, and function in male and female fertility. *Development.* 1995; 121(5):1373–1385. [PubMed: 7789268]
15. Satokata I, Benson G, Maas R. Sexually dimorphic sterility phenotypes in Hoxa10-deficient mice. *Nature.* 1995; 374(6521):460–463. [PubMed: 7700356]
16. Bagot CN, Troy PJ, Taylor HS. Alteration of maternal Hoxa10 expression by in vivo gene transfection affects implantation. *Gene Ther.* 2000; 7(16):1378–1384. [PubMed: 10981664]
17. Daftary GS, Taylor HS. Endocrine regulation of HOX genes. *Endocr Rev.* 2006; 27(4):331–355. [PubMed: 16632680]
18. Salehnia M. Different pattern of pinopodes expression in stimulated mouse endometrium. *Exp Anim.* 2005; 54(4):349–352. [PubMed: 16093648]
19. Nikas G, Drakakis P, Loutradis D, et al. Uterine pinopodes as markers of the 'nidation window' in cycling women receiving exogenous oestradiol and progesterone. *Hum Reprod.* 1995; 10(5):1208–1213. [PubMed: 7657767]
20. Singh MM, Chauhan SC, Trivedi RN, Maitra SC, Kamboj VP. Correlation of pinopod development on uterine luminal epithelial surface with hormonal events and endometrial sensitivity in rat. *Eur J Endocrinol.* 1996; 135(1):107–117. [PubMed: 8765982]
21. 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(3):538–544. [PubMed: 11747087]
22. Lessey BA, Damjanovich L, Coutifaris C, Castelbaum A, Albelda SM, Buck CA. Integrin adhesion molecules in the human endometrium. Correlation with the normal and abnormal menstrual cycle. *J Clin Invest.* 1992; 90(1):188–195. [PubMed: 1378853]
23. Sueoka K, Shiokawa S, Miyazaki T, Kuji N, Tanaka M, Yoshimura Y. Integrins and reproductive physiology: expression and modulation in fertilization, embryogenesis, and implantation. *Fertil Steril.* 1997; 67(5):799–811. [PubMed: 9130881]
24. 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(3):571–579. [PubMed: 11875117]
25. Hustin J, Philippe E, Teisner B, Grudzinskas JG. Immunohistochemical localization of two endometrial proteins in the early days of human pregnancy. *Placenta.* 1994; 15(7):701–708. [PubMed: 7530848]
26. Irwin JC, Suen LF, Faessen GH, Popovici RM, Giudice LC. Insulin-like growth factor (IGF)-II inhibition of endometrial stromal cell tissue inhibitor of metalloproteinase-3 and IGF-binding protein-1 suggests paracrine interactions at the decidua:trophoblast interface during human implantation. *J Clin Endocrinol Metab.* 2001; 86(5):2060–2064. [PubMed: 11344207]
27. Foucher I, Volovitch M, Frain M, et al. Hoxa5 over-expression correlates with IGFBP1 upregulation and postnatal dwarfism: evidence for an interaction between Hoxa5 and Forkhead box transcription factors. *Development.* 2002; 129(17):4065–4074. [PubMed: 12163409]
28. Kim JJ, Jaffe RC, Fazleabas AT. Insulin-like growth factor binding protein-1 expression in baboon endometrial stromal cells: regulation by filamentous actin and requirement for de novo protein synthesis. *Endocrinology.* 1999; 140(2):997–1004. [PubMed: 9927334]
29. Kim JJ, Taylor HS, Lu Z, et al. Altered expression of HOXA10 in endometriosis: potential role in decidualization. *Mol Hum Reprod.* 2007; 13(5):323–332. [PubMed: 17350963]
30. Lim H, Paria BC, Das SK, et al. Multiple female reproductive failures in cyclooxygenase 2-deficient mice. *Cell.* 1997; 91(2):197–208. [PubMed: 9346237]
31. Lim H, Ma L, Ma WG, Maas RL, Dey SK. Hoxa-10 regulates uterine stromal cell responsiveness to progesterone during implantation and decidualization in the mouse. *Mol Endocrinol.* 1999; 13(6):1005–1017. [PubMed: 10379898]

32. 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(1):238–243. [PubMed: 12519859]
33. Daftary GS, Taylor HS. Hydrosalpinx fluid diminishes endometrial cell HOXA10 expression. *Fertil Steril.* 2002; 78(3):577–580. [PubMed: 12215336]
34. Rackow BW, Taylor HS. Submucosal uterine leiomyomas have a global effect on molecular determinants of endometrial receptivity. *Fertil Steril.* June 12.2008
35. 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(5):1328–1331. [PubMed: 10325287]
36. Houston DE. Evidence for the risk of pelvic endometriosis by age, race and socioeconomic status. *Epidemiol Rev.* 1984; 6:167–191. [PubMed: 6386501]
37. Strathy JH, Molgaard CA, Coulam CB, Melton LJ III. Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women. *Fertil Steril.* 1982; 38(6):667–672. [PubMed: 6216124]
38. Simón C, Gutiérrez A, Vidal A, et al. Outcome of patients with endometriosis in assisted reproduction: results from invitro fertilization and oocyte donation. *Hum Reprod.* 1994; 9(4):725–729. [PubMed: 8046030]
39. Tummon IS, Maclin VM, Radwanska E, Binor Z, Dmowski WP. Occult ovulatory dysfunction in women with minimal endometriosis or unexplained infertility. *Fertil Steril.* 1988; 50(5):716–720. [PubMed: 3181483]
40. Ulukus M, Cakmak H, Arici A. The role of endometrium in endometriosis. *J Soc Gynecol Investig.* 2006; 13(7):467–476.
41. Kao LC, Tulac S, Lobo S, et al. Global gene profiling in human endometrium during the window of implantation. *Endocrinology.* 2002; 143(6):2119–2138. [PubMed: 12021176]
42. Metzger DA, Olive DL, Haney AF. Limited hormonal responsiveness of ectopic endometrium: histologic correlation with intrauterine endometrium. *Hum Pathol.* 1988; 19(12):1417–1424. [PubMed: 3192206]
43. Winkel CA, Scialli AR. Medical and surgical therapies for pain associated with endometriosis. *J Womens Health Gend Based Med.* 2001; 10(2):137–162. [PubMed: 11268298]
44. Kastner P, Krust A, Turcotte B, et al. Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. *EMBO J.* 1990; 9(5):1603–1614. [PubMed: 2328727]
45. Horwitz KB, Alexander PS. In situ photolinked nuclear progesterone receptors of human breast cancer cells: subunit molecular weights after transformation and translocation. *Endocrinology.* 1983; 113(6):2195–2201. [PubMed: 6685620]
46. Mote PA, Balleine RL, McGowan EM, Clarke CL. Colocalization of progesterone receptors A and B by dual immunofluorescent histochemistry in human endometrium during the menstrual cycle. *J Clin Endocrinol Metab.* 1999; 84(8):2963–2971. [PubMed: 10443705]
47. Okulicz WC, Savasta AM, Hoberg LM, Longcope C. Immunofluorescent analysis of estrogen induction of progesterone receptor in the rhesus uterus. *Endocrinology.* 1989; 125(2):930–934. [PubMed: 2666107]
48. Mulac-Jericevic B, Lydon JP, DeMayo FJ, Conneely OM. Defective mammary gland morphogenesis in mice lacking the progesterone receptor B isoform. *Proc Natl Acad Sci U S A.* 2003; 100(17):9744–9749. [PubMed: 12897242]
49. Mulac-Jericevic B, Mullinax RA, DeMayo FJ, Lydon JP, Conneely OM. Subgroup of reproductive functions of progesterone mediated by progesterone receptor-B isoform. *Science.* 2000; 289(5485):1751–1754. [PubMed: 10976068]
50. Lee B, Du H, Taylor HS. Experimental murine endometriosis induces DNA methylation and altered gene expression in eutopic endometrium. *Biol Reprod.* 2009; 80(1):79–85. [PubMed: 18799756]
51. Fazleabas AT, Brudney A, Chai D, Langoi D, Bulun SE. Steroid receptor and aromatase expression in baboon endometriotic lesions. *Fertil Steril.* 2003; 80(Suppl 2):820–827. [PubMed: 14505759]

52. Burney RO, Talbi S, Hamilton AE, et al. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. *Endocrinology*. 2007; 148(8):3814–3826. [PubMed: 17510236]
53. Kamat AA, Younes PS, Sayeeduddin M, Wheeler TM, Simpson JL, Agoulnik AI. Protein expression profiling of endometriosis: validation of 2-mm tissue microarrays. *Fertil Steril*. 2004; 82(6):1681–1683. [PubMed: 15589880]
54. Kao LC, Germeyer A, Tulac S, et al. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. *Endocrinology*. 2003; 144(7):2870–2881. [PubMed: 12810542]
55. Klemmt PA, Carver JG, Kennedy SH, Koninckx PR, Mardon HJ. Stromal cells from endometriotic lesions and endometrium from women with endometriosis have reduced decidualization capacity. *Fertil Steril*. 2006; 85(3):564–572. [PubMed: 16500320]
56. Lessey BA, Castelbaum AJ, Sawin SW, et al. Aberrant integrin expression in the endometrium of women with endometriosis. *J Clin Endocrinol Metab*. 1994; 79(2):643–649. [PubMed: 7519194]
57. Vitiello D, Kodaman PH, Taylor HS. HOX genes in implantation. *Semin Reprod Med*. 2007; 25(6):431–436. [PubMed: 17960527]
58. 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):1–13. [PubMed: 12482956]
59. Daftary GS, Taylor HS. EMX2 gene expression in the female reproductive tract and aberrant expression in the endometrium of patients with endometriosis. *J Clin Endocrinol Metab*. 2004; 89(5):2390–2396. [PubMed: 15126568]
60. Taylor HS, Fei X. Emx2 regulates mammalian reproduction by altering endometrial cell proliferation. *Mol Endocrinol*. 2005; 19(11):2839–2846. [PubMed: 15994197]
61. Reik W, Dean W, Walter J. Epigenetic reprogramming in mammalian development. *Science*. 2001; 293(5532):1089–1093. [PubMed: 11498579]
62. Ehrlich M. Expression of various genes is controlled by DNA methylation during mammalian development. *J Cell Biochem*. 2003; 88(5):899–910. [PubMed: 12616529]
63. Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. *Nat Rev Genet*. 2002; 3(6):415–428. [PubMed: 12042769]
64. Robertson KD. DNA methylation and human disease. *Nat Rev Genet*. 2005; 6(8):597–610. [PubMed: 16136652]
65. Wu Y, Halverson G, Basir Z, Strawn E, Yan P, Guo SW. Aberrant methylation at HOXA10 may be responsible for its aberrant expression in the endometrium of patients with endometriosis. *Am J Obstet Gynecol*. 2005; 193(2):371–380. [PubMed: 16098858]
66. Wu Y, Strawn E, Basir Z, Halverson G, Guo SW. Aberrant expression of deoxyribonucleic acid methyltransferases DNMT1, DNMT3A, and DNMT3B in women with endometriosis. *Fertil Steril*. 2007; 87(1):24–32. [PubMed: 17081533]