Uterine polyps, adenomyosis, leiomyomas, and endometrial receptivity

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Endometrial polyps, adenomyosis, and leiomyomas are commonly encountered abnormalities frequently found in both fertile women and those with infertility. The clinician is frequently challenged to determine which of these entities, when found, is likely to impair fertility, and which are "innocent bystanders" unrelated to the problem at hand. Although removing an endometrial polyp may be seen as a relatively benign and safe intervention, myomectomy, and in particular adenomyomectomy, can be substantive surgical procedures, associated with their own potential for disrupting fertility. One of the mechanisms thought to be involved when these entities are contributing to infertility is an adverse impact on endometrial receptivity. Indeed polyps, adenomyosis, and leiomyomas have all been associated with an increased likelihood of abnormal endometrial molecular expressions thought to impair implantation and early embryo development. This review is designed to examine the relationship of these common entities to endometrial receptivity and to identify evidence gaps that should be considered when strategizing research initiatives. It is apparent that we have the tools necessary to fill these gaps, but it will be necessary to approach the issue in a strategic and coordinated fashion. It is likely that we will have to recognize the limitations of imaging alone and look to the evidence-based addition of molecular analysis to provide the individualized phenotyping of disease necessary for patient-specific treatment decisions. (Fertil Steril® 2019;111:629–40. ©2019 by American Society for Reproductive Medicine.)

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Successful implantation is the result of a series of complex interactions between the decidualized endometrium and the early embryo. It is apparent that structural abnormalities of the uterus can be associated with a disruption of this essential process by impeding some combination of embryo transport and subsequent implantation into the endometrium. However, it is also clear that some structural abnormalities may not have any apparent impact on these aspects of normal fertility, a circumstance that begs a number of questions. How do we determine when, and when not, to intervene when structural anomalies are identified in women with infertility or recurrent early pregnancy loss? Has our improved ability to diagnose abnormalities such as polyps, adenomyosis, and leiomyomas placed infertile women in jeopardy from unnecessary surgery and other interventions? If interventions are required or recommended, what is the role for medical therapy? For traditional surgery? For new image-guided and other techniques?

This article is designed to review what is currently known about the impact of endometrial polyps, adenomyosis, and uterine leiomyomas on factors associated with implantation, and in particular, endometrial receptivity. A systematic review has been performed to evaluate the available literature for evidence regarding the influence of these entities on implantation. PubMed was searched for each of the entities (polyps, adenomyosis, and leiomyomas) using the following terms: endometrial, polyps, adenomyosis, leiomyomas, fibroids and endometrial receptivity, and implantation and implantation failure. Searches were reviewed initially for relevance, and then abstracts were obtained to identify those that seemed to represent receptivity-related studies for one or more of the three entities. When abstracts were deemed relevant the full article was obtained and reviewed. Additional articles were identified by review of bibliographies of full-text papers. A total of 54 citations were reviewed for endometrial polyps, 92 for adenomyosis, and 148 that were related to leiomyomas. From these were

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identified 5 for polyps, 24 for adenomyosis, and 11 for leiomyomas that related to implantation, focusing on but not limited to endometrial receptivity, generally based on molecular expressions or uterine peristaltic activity.

Before we launch into the review of what is known about the impact of adenomyosis, polyps, and leiomyomas on endometrial receptivity, it seems appropriate to review what is known about endometrial receptivity itself.

ENDOMETRIAL RECEPTIVITY

The process of implantation requires coordinated and synchronous development of the embryo and an endometrium that is receptive to implantation, optimally between 6 and 10 days after ovulation (1). For the endometrium, the stage is set by exposure to E_2 during the 2 weeks or so before ovulation, following which the process of decidualization begins, promoted by the production and systemic release of P from the corpus luteum. The histopathologically visible process of decidualization reflects a largely invisible and complex yet rigorously coordinated set of molecular events that are essential to endometrial receptivity.

Critical to these processes are homeobox (Hox) genes. The family of 39 Hox genes encodes proteins that act as transcription factors that are not only important embryologically for axial development but are also pivotal to the normal development of the female reproductive tract (2). They also are critical to functional endometrial development during the menstrual cycle, and in particular to endometrial receptivity. Hox-A10 and -A11 seem to be the most important; both are expressed in the endometrium during the proliferative phase of the cycle and peak in the mid-secretory phase under the influence of P (3, 4). In addition, both have been demonstrated deficient in the secretory phase of women with low rates of implantation (4, 5). Both HOXA-10 and HOXA-11 influence downstream factors influencing endometrial receptivity by activating or repressing target genes, such as β3-integrin and Emx2 (2).

A number of other parallel and related endometrial events seem critical to enhanced endometrial receptivity. There exists a complex interplay among autocrine and paracrine factors that include a spectrum of cytokines and chemochines as well as their receptors and secondary messengers. During the decidualization process there are demonstrable local increases in prostaglandins and vascular endothelial growth factor, as well as extravasation of immune cells, primarly comprising macrophages and natural killer (NK) cells (6). Also witnessed on the endometrial surface is increased pinopode expression (7) and expression of cell adhesion molecules, such as integrin and osteopontin (8, 9).

When it is expelled into the endometrial cavity from the fallopian tube, the free-floating blastocyst is approximately 0.2 mm in diameter. It is apparent that there is bidirectional communication between the "preimplanted" embryo and endometrium that coordinates and facilitates impantation (10). After "hatching" from the zona pellucida, and in the region of the inner call mass (11), the early embryo seems to attach to the endometrium in a region of increased pinopode expression.

It seems that successful embryo implantation is the consequence of an invasive process that is facilitated by a number of factors, including cytokines, morphogens, steroid hormones, adhesion molecules, and growth and transcription factors. Macrophages, largely the product of P, locally produce cytokines such as leukocyte inhibitory factor (LIF) and interleukin (IL)-11 that seem to be important to embryo implantation (12, 13), possibly via the gp130 signaling pathway (14–16). After attachment of the embryo to the endometrium, IL-11 plays a role in the regulation of trophoblast invasion; deficiencies are associated with reduced local levels of NK cells in the secretory endometrium (12) and, at least in mice, early pregnancy loss (17). The NK cells are the dominant immune cells during the window of implantation (WOI) and seem to be important reglators of immunotolerance, angiogenesis (via vascular endothelial growth factor and placental growth factor), and trophoblast migration and invasion (18, 19). Growth factors are also important; for example, heparin-binding epidermal growth factor is a transforming growth factor (TGF)-β family protein that responds to P to induce the secretion of bone morphogenetic protein (BMP)-2, critical to the process of decidualization (20–22). Reduced secretion of BMP-2 is associated with reduced endometrial stromal cell expression of HOXA-10 and LIF (23).

Another important contributor to conception and implantation is uterine peristalsis. Indeed, disorders of uterine peristalsis may contribute to the pathogenesis of a number of disorders, such as endometriosis and adenomyosis, and may impair sperm and embryo transport as well as implantation (24). This will be discussed in more detail later.

IMPACT OF UTERINE ANOMOLIES (POLYPS, ADENOMYOSIS, LEIOMYOMAS) ON IMPLANTATION

Each of these disorders is commonly found in both normal and infertile women. It can be estimated that, during the reproductive years, endometrial polyps can be identified in 8%–12% of women (25, 26), adenomyosis in 35% (27), and, by age 50 years, leiomyomas in almost 70% of Caucasians and in more than 80% of women of African ancestry (28). It is also apparent that their mere presence does not imply a negative impact on fertility in general and endometrial receptivity in particular. So a fundamental question facing the clinician is, "When do polyps, adenomyosis, and leiomyomas negatively impact fertility and early pregnancy development?" Presented a different way, when may these lesions adversely impact the molecular and other factors necessary for blastocyst attachment and normal developent within the decidualized endometrium? When do they result in abnormal expressions of receptivity genes, growth factors, cytokines, and other factors, including myometrial contractility, in a fashion that impairs implantation?

Polyps

Endometrial polyps are localized endothelial tumors comprising endometrial glands, stroma, blood vessels, and, typically, fibrous tissue. Their morphology varies

considerably, from millimeters to centimeters in largest dimension, sessile or pedunculated in shape, and single or multiple in number. When followed for a year, spontaneous resolution may occur in up to 27% (26).

Polyps and infertility. Endometrial polyps are common in those with infertility (29, 30), with a prevalence as high as 32% (31). However, the sometimes similar prevalence of endometrial polyps in normal and infertile women raises questions regarding the role, if any, that endometrial polyps have in the pathogenesis of infertility.

Impact of polypectomy. One approach to estimating the relationship between endometrial polyps and infertility is to study the impact of polypectomy on infertile women. There is one randomized trial, involving 215 subjects, designed to evaluate the impact of hysteroscopic polypectomy on fertility when performed before IUI (32–34). Those randomized to hysteroscopic polypectomy were twice as likely to become pregnant as those in the control group, who did not undergo polypectomy. Another prospective, comparative, but nonrandomized trial involving 171 women also demonstrated that hysteroscopic endometrial polypectomy improved IUI results (35). Two other comparative studies, not randomized, demonstrated no benefit to hysteroscopic polypectomy (36, 37). In one of these studies, removal of polyps less than 1.5 cm in maximum diameter did not improve the results of ET (37).

Although the evidence linking hysteroscopic polypectomy to IVF-ET success rates is conflicting, there has been investigation regarding the appropriate timing of ET after polypectomy. In a nonrandomized study of 487 patients, there was no difference when ET was performed after one, two to three, or more than three subsequent cycles in the rates of implantation (42.4%, 41.2%, 42.1%), clinical pregnancy (48.5%, 48.3%, 48.6%), spontaneous pregnancy loss (4.56%, 4.65%, 4.05%), and live bith (44.0%, 43.6%, 44.6%) (38).

Impact on endometrial molecular expressions. The potential mechanisms whereby endometrial polyps could adversely impact fertility include both mechanical interference and the release of molecules that adversely effect sperm transport or embryo implantation. There exists evidence of increased levels of glycodelin (39), aromatase (40), inflammatory markers (41), and reduced levels of HOXA-10 and -11 messenger RNA (42); the latter, as discussed, molecular markers associated with endometrial receptivity. No studies were found comparing these expressions before and after polypectomy.

Adenomyosis

Definition and background. Adenomyosis is the presence of ectopic, nonneoplastic, endometrial glands and stroma in the myometrium. Typically, the ectopic endometrium is surrounded by hypertrophic and hyperplastic myometrium. Although adenomyosis was first described in 1860 by Carl von Rokitansky (43), before the descriptions of endometriosis, until relatively recently it could only be reliably diagnosed by hysterectomy. Consequently, because endometriosis could be diagnosed by laparoscopy, investigation into the role of adenomyosis amidst a spectrum of gynecologic disorders, including infertility and recurrent pregnancy loss, was obscured. With the advent of high-resolution ultrasound and the development of magnetic resonance imaging (MRI), the diagnosis of adenomyosis can now be relatively reliably made absent hysterectomy (44–47), a circumstance that has created the opportunity to investigate its pathogenesis, molecular expressions, and clinical impact.

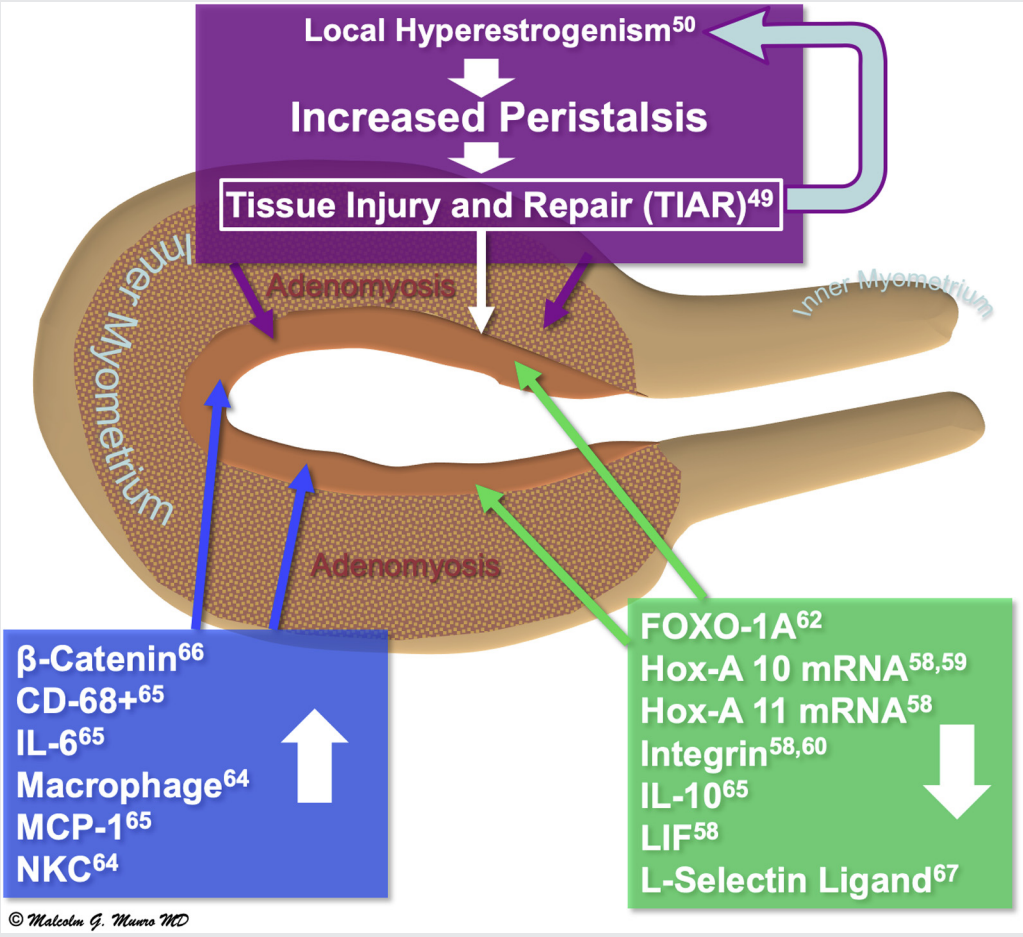
Pathogenesis. There exist a number of hypotheses regarding the pathogenesis of adenomyosis, and it is likely that more than one is responsible for the spectrum of the recognized disease phenotypes. The disorder can manifest as one or a combination of thickening of the internal myometrium, areas of focal or diffuse disease, and involvement of the outer myometrium. One hypothesis is that trauma occurs at the endometrial myometrial interface fostered (fostered by increased peristalsis) increased peristalsis of the junctional zone (48). This process results in local trauma and a repair meachanism (tissue injury and repair) that results in increased local levels of E_2 (49), a circumstance that further promotes hyperperistalsis and increasing local damage that allows "invasion" of endometrium into the myometrium (50, 51) (Fig. 1). When outer myometrial adenomyosis exists in isolation it has been hypothesized that it may occur secondary to invasion of endometriosis, either from posterior or anterior sources (52). Relatively recent genetic evidence suggests that there are more than 1,000 abnormally up-regulated or down-regulated genes in the eutopic endometrium of women with adenomyosis when compared with controls (53).

Adenomyosis and infertility. Although evidence has been conflicting, there seems to be an overall negative impact of adenomyosis on fertility (54) and, in particular, assisted reproductive technology outcomes (55). It is postulated that adenomyosis may contribute to infertility by changing the normal myometrial architecture and function by altering normal uterine peristalsis and by negatively impacting sperm transport. However, and perhaps more importantly, adenomyosis may result in disordered decidualization manifesting in reduced endometrial receptivity, a circumstance associated with the presence of defects or other abnormalities in measurable implantation markers.

The adenomyosis–infertility story is not a simple one. It is apparent that, in some women, adenomyosis seems inert, with no impact on reproductive function. For example, there is evidence that women with adenomyosis that is asymptomatic have ET success rates similar to those in women without adenomyosis (56). So one important caveat is that there may well be a spectrum of manifestations of adenomyosis, a circumstance that may affect our interpretation of studies unless they are controlled for the presence of symptoms, disease location and burden, and other potentially relevant phenotypic features of the disease (57).

Molecular impact. There exists an evolving body of evidence examining the impact of adenomyosis on the molecular expressions thought to be important for optimal endometrial receptivity (Fig. 1). Hox-A10 gene expression can be decreased both in the mouse model with experimental adenomyosis (58) and in the secretory-phase endometrium of

FIGURE 1



Adenomyosis may adversely impact fertility by its impact on myometrial contractility and/or via altered molecular expressions in the endometrium. Local hyperestrogenism is thought to be related to increased and dysfunctional peristalsis of the inner myometrium, leading to disruption of the integrity of the endometrial–myometrial interface, thereby facilitating growth of endometrium into the myometrium. This process is self-propagating as the mechanism of repair itself results in increased local levels of E_2. Adenomyosis may also reduce endometrial receptivity when it is associated with abnormal molecular expressionsm, such as reduced levels of HOXA-10, -11 and increases or decreases in other factors thought or known to be important for implantation and early embryo development.

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women with adenomyosis (59). Dysregulation of endometrial LIF is also seen during the WOI (58, 60, 61). NR4A receptors drive decidualization of human endometrial stromal cells by transcriptional activation of FOXO1A, and both NR4A and *FOXO1A* are down-regulated in adenomyotic tissue, a circumstance that impairs decidualization (62). Some inflammatory markers are increased, such as IL-1β and corticotropin-releasing hormone (63), as well as NK cells, macrophages (64), and a spectrum of cytokines (65). The role of the integrin family of cell adhesion receptors is related to the cell to cell interactions that occur between the conceptus and the endometrium that involve the ECM. Also reported are increased levels of β-catenin (66) and L-selectin (67), proteins that in part are involved with regulation of cell to cell adhesion. The normal elevations of integrin beta-3 and osteopontin are reduced in women with adenomyosis (68), and lower serum osteopontin levels have been reported in women with "focal" disease (69).

There is also evidence of decreased estrogen (E) metabolism in eutopic endometrium (70). Increased E resistance also is associated with a down-regulation of P receptors and resulting P resistance (70, 71) and decreased P receptor isoform B (72), perhaps related to methylation of the promoter (73). Overall this suggests that adenomyosis may be be related to epigenetic dysregulation of genes (73, 74).

Uterine peristalsis. As discussed above, the inner myometrium, an entity embryologically distinct from the outer myometrial layers, is the structure that largely contributes to uterine peristalsis. The thickening of this zone, seen best with MRI, is a feature found in many if not most women with adenomyosis. It does not take much to imagine that involvement of this muscular layer with eutopic glands and

stroma might adversely impact the normal peristaltic activity thought necessary to facilitate sperm and embryo transport within the endometrial cavity. An elegant experiment by Kissler et al. (75), using radionucleotide techniques, demonstrated that normal ipsilateral (to the follicle) uterotubal transport was suppressed in women with diffuse adenomyosis.

Evidence exists that higher uterine contraction frequencies in natural (76) and stimulated cycles (77, 78), as well as around ET (79, 80), are associated with a reduction in conception, implantation, and live birth rates. There are fewer data evaluating the impact of adenomyosis on periimplantation uterine peristalsis, and the frequent coexistence of endometriosis and adenomyosis has made interpretation of the available literature difficult (24).

Local hyperestrogenism is thought to lead to increased peristalsis of the subendometrial myometrium (inner myometrium or junctional zone), imposing supraphysiologic mechanical strain on the cells near the fundo-cornual raphe that activates the tissue injury and repair system focally, with further local production of E_2 (50) (Fig. 1). The suggested mechanism is activation of aromatase and sulphatase because there are increased levels of E_2 in menstual blood but not peripheral blood of women with adenomyosis (81). Paracrine focal E production, possibly mediated by endometrial oxytocin, increases the uterine peristalsis.

Impact of therapy on adenomyosis-related infertility. There are limited data evaluating the impact of medical therapy, surgical removal, and other procedural interventions on adenomyosis-related infertility. Consequently, there is little evidence available to help understand the relationship between adenomyosis and endometrial receptivity. Nonetheless, there is some evidence from comparative but nonrandomized studies that down-regulation with GnRH agonists for 1 to 3 months may improve pregnancy rates after frozen embryo transfer in women with adenomyosis (82, 83). Given evidence that long-term GnRH agonist therapy can result in reduced local manifestations of adenomyosis, including reduced tissue inflammation and angiogenesis as well as an increased apoptotic index (84), one could hypothesize that this approach could improve endometrial receptivity. Potential mechanisms could also include reducing local hyperestrogenism thought to be related to dysfunctional inner myometrial peristalsis discussed previously.

High-intensity focused ultrasound has been the subject of a number of case reports and small uncontrolled studies evaluating its impact on fertility and pregnancy performance (85, 86). These studies suggest, but do not prove, that high-intensity focused ultrasound may improve pregnancy rates by reducing disease burden, and there have been no molecular studies evaluating the impact on markers of endometrial receptivity. No relevant investigation has been identified related to other image-guided therapy, adenomyosis, and infertility.

There have been a number of studies evaluating the impact of adenomyomectomy or adenomyosis resection on fertility that collectively have been the subject of systematic reviews and, in some cases, meta-analysis (87–90). Although there seems to be an improvement in fertility outcomes, no comparative studies exist, and there do not seem to be any evaluating the impact of conservative surgery on surrogate outcomes, such as endometrial expression of markers associated with receptivity.

Leiomyomas

Pathogenesis. Leiomyomas, often called fibroids or simply myomas, are believed to be derived from a single leiomyoma stem cell (91). Such cells seem to develop after a genetic "hit" on a normal myometrial cell that results in a point mutation in the mediator complex subunit 12 (MED12) gene or the high-mobility group AT-hook2 (*HMGA2*) gene. The latter resides on the long arm of chromosome 12 (91, 92). There are three cell populations in leiomyomas: well differentiated, intermediate differentiation, and fibroid stem cells. Tumor growth may vary depending on the relative proportions, so that it is more rapid when there exists a higher proportion of fibroid stem cells (93). Endocrine-disrupting chemicals, potentially altered by environmental, racial, or ethnic factors, may contribute to these genetic alterations in myometrial stem cells (94–96). Tumor-initiating myometrial stem cells are more prevalent in women of African ancestry with fibroids and lowest in Caucasians without uterine leiomyomas (97).

Leiomyomas contain E_2 receptors, and E_2 is associated with proliferation of uterine smooth muscle cells (98, 99). This allows for a response to systemically released as well as to locally derived Es, including those that are the result of conversion from androgens via the effect of aromatase (100). However, leiomyoma stem cells express low levels of E and P receptors, a circumstance that could suggest a paracrine mechanism for control of growth.

A signaling pathway seemingly important in leiomyoma growth is the Wingless Type (WNT)/β-catenin pathway that targets the MED12 subunit that, if mutated, can result in inhibition of β-catenin transactivation in response to WNT signaling. Activation of the WNT/β-catenin pathway is associated with increased levels of TGF-β3, a factor secreted in relatively high levels by leiomyomas under gonadal steroid stimulation (101). It has been demonstrated that TGF-β3 plays a role in cellular proliferation, deposition of extracellular matrix (102), and paracrine effects on endometrial stromal and columnar cells (23, 42, 103). It also functions to mediate the production of BMP-2, which has been shown to mediate HOXA-10 expression.

Ten years ago a systematic review demonstrated that submucous leiomyomas were associated with lower implanation rates than in women without such tumors (3.0%–11.5% vs. 14%–30%) and an increased risk of early pregnancy loss (47% vs. 22%) (104)—a notion supported by other investigators (105, 106). This hypothesis was also supported by a meta-analysis by Pritts et al. (107). Intramural leiomyomas, on the other hand, have a questionable impact on fecundity. Although there is some evidence that they are associated with increasing rates of pregnancy loss and reduced fecundity (107, 108), other prospective studies show no such relationship (109, 110).

Submucous leiomyoma impact. There are a number of potential mechanisms whereby leiomyomas may adversely affect implantiation. These include abnormally increased uterine contractility and disturbances in endometrial cytokine expression, as well as abnormal vascularization and chronic endometrial inflammation.

One mechanism that has undergone substantial evaluation is down-regulation of BMP-2 receptors and resulting BMP-2 resistance secondary to TGF-β3 produced by leiomyomas adjacent to the endometrium. There is evidence that HOXA-10 levels are reduced in the endometrium of women with submucous leiomyomas, not only in the tissue that is over the leiomyomas themselves but also in the endometrium elsewhere in the endometrial cavity (42) (Fig. 2). This implies the presence of a signaling mechanism that is thought to be TGF-β3, which has been demonstrated to be increased in the endometrium in women with submucous myomas, that results in down-regulation of BMP-2 receptor expression in endometrial stromal cells and resulting resistance to MBP-2 (103). This mechanism has been demonstrated to be associated with the reduced expression of factors such as HOXA-10 and LIF and may explain defective decidualization and reduced implantation success (23).

In the presence of submucous leiomyomas the normal luteal phase increase in LIF is "blunted" (111), and deficiencies have been shown to be associated with unexplaned infertility and recurrent abortion (112). There is evidence that IL-II levels are reduced in the WOI in women with submucous leiomyomas (111).

Other investigators have demonstrated differences between inflammatory markers (macrophages, monocyte chemotactic protein-1, and prostaglandin-F2α) of women with submucous myomas, although these have not been correlated with implantation or pregnancy outcomes (6).

Intramural myomas. Studies evaluating the role of "intramural" leiomyomas in the genesis of infertility in general, and abnormalities in endometrial receptivity in particular, are confounded by the variable definitions of intramural, and of the methodology used to define the location of a leiomyoma itself. Intramural myomas, by some definitions, require the interposition of some amount of myometrium between the medial border of the leiomyoma and the endometrium, whereas others do not make this distinction and include tumors that may abut the endometrium, even if they do not distort the endometrial cavity. The method of making the diagnosis—ultrasound, hysteroscopy, or MRI—may well impact the accuracy of the diagnosis, even if the definitions are agreed upon. The International Federation of Gynecology and Obstetrics (FIGO) subclassification system for leiomyomas (Fig. 3) has addressed this issue (113, 114), but relatively few studies have used this system or an equivalent definition when reporting methods for selecting women with intramural myomas. Of course, there may be other confounders as well, including tumor volume, number, genetic heterogenity, and even the thickness of intervening myometrium, that could explain differential expression of molecules with an influence on endometrial receptivity.

The issue of defining the intramural leiomyoma should be considered when interpreting the available evidence. For example, although there is some evidence that there is an adverse effect of intramural myomas on implantation rates (105, 108, 115–118), including a systematic review (119), other studies, including another systematic review (120), have failed to support this hypothesis (110, 121–125). Some studies have also shown that there is decreased HOXA-10 expression during the WOI, as well as lower endometrial levels of E-cahedrin, a cell adhesion molecule in women with intramural leiomyomas (126). Other evidence suggests that subserosal leiomyomas and intramural tumors of $\leq$4 cm in diameter do not impact IVF-ET rates but that intramural myomas $>$4 cm in diameter were associated with reduced pregnancy rates (124), findings similar to those reported by others (104, 107, 110).

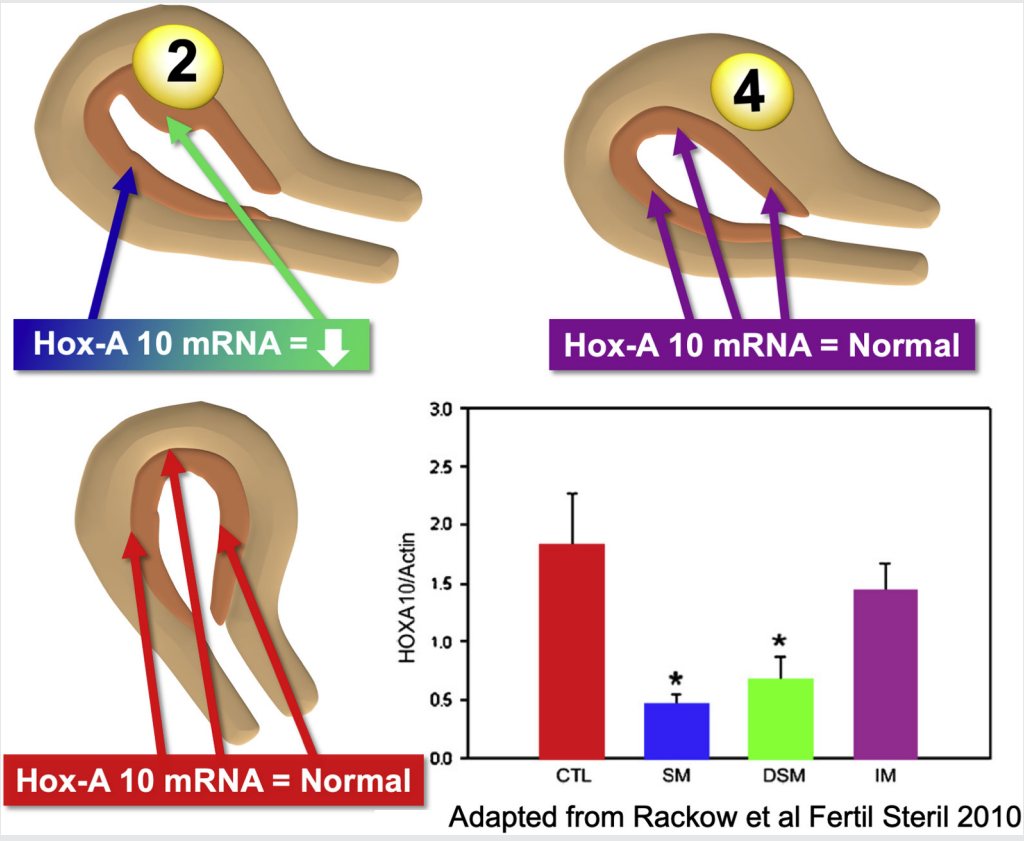
Although there may be changes in some endometrial genes, expressions related to receptivity were not altered in a large retrospective study that also correlated IVF-ET success, which did not vary regardless of leiomyoma size or number (127). Although there were no clinical correlations, similar results were published by investigators from University of California, San Francisco, who evaluated endometrial gene expression and function in women with intramural myomas; although there were dysregulated transcripts, compared with controls, there were no differences in the expression of receptivity and decidualization markers (128).

Given the evidence that contact with the endometrium is associated with impaired decidualization, it could be hypothesized that "intramural" myomas that are in contact with the endometrium may have a very different impact on implantation than those with myometrium between the myoma and the endometrium. For example, a recent study that used the FIGO classification system demonstrated that single or multiple type 3 leiomyomas, $\geq$2 cm in diameter, individually or collectively, were associated with a lower implantation rate as well as a reduced rate of clinical pregnancy and delivery (129). Biochemical pregnancy (29.1% vs. 51.4%), implantation (22.7% vs. 34.4%), clinical pregnancy (27.8% vs. 43.9%), and live birth rates (21.2% vs. 34.4%) were significantly reduced in the women with type 3 myomas compared with controls.

It has also not yet been demonstrated that myomectomy improves pregnancy rates associated with type 3 leiomyomas (107, 120). This suggests that the definition of "intramural" should be reviewed and that the FIGO leiomyoma classification system should be considered when designing future investigation.

Nonspecific myomas. There is a body of evidence examining leiomyomas not specific to location. For example, although fibroid size may be a determining factor, it was not shown to be relevant in a meta-analysis performed and reported in 2009 (107). There have been studies on endometrial gene expression based on leiomyoma size, demonstrating that three genes (glycodelin and aldehyde dehydrogenase 3 family member B2) were dysregulated when intramural myomas were $>$5 cm in diameter, whereas only one (glycodelin) was abnormal when myomas were smaller.

FIGURE 2



Impact of submucous leiomyomas on endometrial Hox-A10 messenger RNA expression. Investigators from Yale University found that submucous leiomyomas were associated with reductions in Hox-A10 expression both over the leiomyoma and throughout the endometrial cavity (*upper left*). On the other hand, the Hox-A10 expression in women with intramural myomas (*upper right*) was similar to that of women without any leiomyomas (*lower left*). Adapted from Rackow et al. (42), with permission.

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Mechanical stretch of the endometrium and/or myometrium can manifest in varying gene expressions (130–132). Abnormal uterine contractions have been demonstrated in the luteal phase of women with leiomyomas, using cine MRI (133). During the WOI in women with "intramural fibroids," high-frequency peristalsis, as opposed to low frequency contractions, have been associated with 0 of 22 pregnancies, as opposed to 10 of 29 (134).

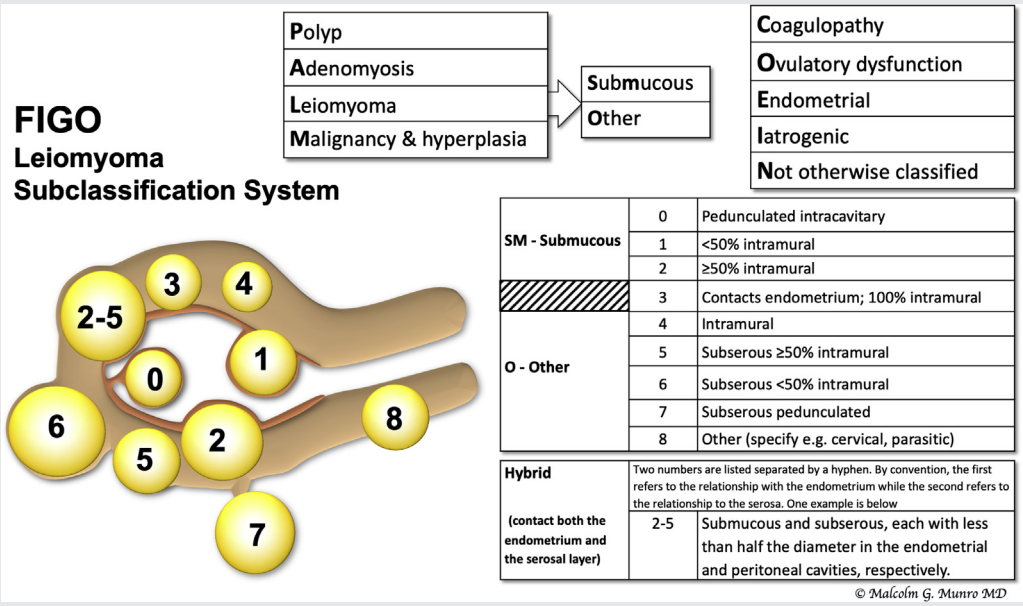
Impact of myomectomy and image-guided therapy. There is evidence from a meta-analysis of randomized trials that hysteroscopic myomectomy improves spontaneous pregnancy rates by 21%–39%. However even this study had too few subjects to achieve significance (34), although a subsequent randomized controlled trial came to the same conclusions (135). Interestingly, in the one study that has evaluated surrogate markers for receptivity, intramural but not submucous myomectomy was shown to result in increased HOXA-10 levels (136). No prospective comparative studies could be found.

Although there have been cases series and systematic reviews of pregnancy after radiofrequency ablation (137, 138), MR-guided focused ultrasound (138, 139), and uterine artery embolization (140, 141), none have provided information that would seem to be useful in understanding the relationship between leiomyomas and endometrial receptivity.

SUMMARY: SO WHAT DO WE KNOW?

In review, and especially when we look for them, polyps, adenomyosis, and leiomyomas are found commonly both in women who are symptomatic and in those who are not, and in our patients with infertiity as well as those who conceive and deliver with relative ease. Because of our relative ready access to hysteroscopy, MRI, and high-resolution ultrasound techniques, we can now can more readlly characterize these entities in infertile women and those with recurrent early pregnancy loss. However, the frequent presence of these disorders begs the questions of when and how: When are they clinically relevant, and how do we evaluate women for relevant disease? It is apparent that there exist features of these polyps, adenomyosis, and leiomyomas, beyond their mere presence, that determine when and whether they will manifest

FIGURE 3



The FIGO Leiomyoma Classification System (System 2). This system was developed to guide research and clinical care for women with abnormal uterine bleeding, but the leiomyoma subclassification system applies equally well to research into infertility and reproductive loss (113, 114).

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with symptoms, including infertility and recurrent pregnancy loss. Indeed, it seems likely that we are dealing with disorders that are extremely heterogenous in their impact, in part because of volume, number, and location, but largely related to their molecular impact on the mechanisms of sperm and embryo transport and on implantation and early embryonic developemnt.

So where are we? Endometrial polyps are common, but there is precious little proof that they cause or contribute to infertilty in general and implantation failure in particular. Of course, we have not even defined polyps in a consistent fashion—an observation that points to the need for some sort of universal classification system to provide an infrastructure for research and subsequent clinical management. For example, there may well be differences in the impact on endometrial receptivity of a single 5-mm polyp and that of a cluster of 2-cm lesions filling the endometrial cavity. Our appetite for rigorous research on endometrial polyps may be blunted by the fact that they are easy to remove, especially if the clinician has access to an environment where hysteroscopic polypectomy can be performed in an office setting under local anesthesia.

Adenomyosis remains an enigma. Although overall the evidence suggests that fertility is adversely affected, many investigators using IVF and ET have had a difficult time even identifying any clinical impact of adenomyosis in their subject-patients. I suspect that the investigators from Milan are on to something when they evaluated the impact of asymptomatic adenomyosis on ET success—the asymptomatic women studied seemed to have success reates similar to those of historical controls without symptoms (56). To me, and taking into account the overall impact of adenomyosis on ET success, this points to intrinsic differences in histologically similar disease processes in individuals that likely manifest in some combination of abnormal molecular expressions and dysfunctional myometrial contractility.

Unlike endometrial polyps and even leiomyomas, removing adenomyosis is not easy, so embarking on adenomyomectomy should be done only in women for whom a benefit may exist. Not long ago such surgery would be seen as folly, but it is apparent that women undergoing adenomyomectomy can conceive, although usually with IVF-ET and, at least in diffuse disease, with a greater risk of uterine rupture in later gestations. Our understanding of the impact of medical interventions designed to minimize the abnormal molecular expressions, or image-guided ablative therapy using ultrasound or radiofrequency electrical energy, is currently "embryonic" in terms of their development and assessment, with no good data available regarding appropriate patient selection, relevant patient outcomes, or subsequent pregnancy risks.

Perhaps we know most about the role of leiomyomas on endometrial receptivity—but it is not really much. There is reasonable evidence that submucous leiomyomas produce substances that can alter the endometrial milieu in the midluteal phase in a way that is associated with reduced implantation success. In this regard, it can generally be inferred that removing FIGO type 0, 1, and 2 tumors should improve fertility and that type 5, 6, and 7 tumors are unlikely to have any impact on endometrial receptivity. However, when faced with type 3 and 4 tumors we are currently at a loss, because we are short of proof of any impact but also short of evidence; and every day, women with such leiomyomas are seen by reproductive surgeons and endocrinologists who

have to opine regarding the potential impact of these tumors on endometrial receptivity on the basis of perception rather than evidence-supported measurement of the patient's endometrial environment.

It would seem that the tools are there to measure what is going on in the endometrium and, to an extent, the myometrium. We known that there are molecular alterations—it is time that we put this information to work.

EVIDENCE GAPS AND SUGGESTED RESEARCH

1. General

a. It is likely that all of the polyps, adenomyosis, and leiomyomas' structural entities are heterogenous with respect to their genetic construct and molecular expressions, so the notion that imaging alone can or should be the only means by which interventions should be recommended or avoided seems inadequate. Consequently, molecular testing should be included.
b. Evaluation should be standardized with respect to cycle time and the components of the testing paradigm.
c. Baseline and postintervention molecular evaluation should be considered for all pathologies.
d. The role that all structural anomalies play in periconceptual and peri-implantation uterine peristalisis should be evaluated and should be correlated with molecular and other surrogates.

2. Polyps

a. A universally accepted classification system is necessary to guide design and interpretation of polyp research.
b. Investigation should be undertaken to identify correlations between polyp size, number, location, and appearance and relevant molecular expressions.
c. It will be important to evaluate the impact of polypectomy on women with abnormal receptivity-related molecular expressions in the WOI.

3. Adenomyosis

a. A universally accepted classification system for adenomyosis is needed, one that would facilitate the design and interpretation of both basic and clinical research (such a process is underway at FIGO).
b. Investigators should design studies evaluating the impact of adenomyosis, with and without endometriosis, on uterine peristalsis around spontaneous and stimulated cycles. as well as around embryo transfer.
c. Molecular and other local indicators of impaired endometrial receptivity should be compared with clinical features, such as disease burden, location, and symptoms, including dysmenorrhea and heavy menstrual bleeding.
d. Structured research on the impact of short-term medical therapy on molecular expressions of receptivity and on conception should be a priority.
e. Evaluation of the impact of adenomyomectomy, carefully determining disease burden, and including changes in molecular expressions of endometrial receptivity.

4. Leiomyomas

a. Research should be conducted using the FIGO subclassification system and consistent and accurate methodology for categorizing leiomomas.
b. It is important to repeat and expand upon studies of endometrial receptivity expressions with type 1, 2, 3, and 4 leiomyomas, both over the tumor and elsewhere in the endometrial cavity
c. Pre- and postmyomectomy studies, carefully designed to appropriately categorize leiomyomas by type and other features, should be performed to evaluate and compare changes in endometrial expressions compared with baseline.
d. There should be an evaluation of the impact of novel medical interventions on molecular expressions, including selective P receptor modulators and GnRH antagonists. Such studies should seek to determine whether there is a prolonged effect that persists beyond their systemic impact.
e. There are a number of new procedural interventions for leiomyomas that have undergone evaluation and regulatory approval based on changes in uterine bleeding. These should be evaluated from a fertility perspective and include transabdominal and transcervical radiofrequency ablation, as well as MR-guided focused ultrasound. Such studies should include baseline and postintervention measures of endometrial receptivity.
f. With the advent of agents designed to provide long term medical therapy for leiomyomas, it will be important to evaluate their role in secondary prevention following myomectomy, particularly in young patients.

REFERENCES

1. Achache H, Revel A. Endometrial receptivity markers, the journey to successful embryo implantation. Hum Reprod Update 2006;12:731–46.
2. Du H, Taylor HS. The role of Hox genes in female reproductive tract development, adult runction, and fertility. Cold Spring Harb Perspect Med 2015; 6:a023002.
3. 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.
4. 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.
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.
6. Miura S, Khan KN, Kitajima M, Hiraki K, Moriyama S, Masuzaki H, et al. Differential infiltration of macrophages and prostaglandin production by different uterine leiomyomas. Hum Reprod 2006;21:2545–54.
7. Bentin-Ley U. Relevance of endometrial pinopodes for human blastocyst implantation. Hum Reprod 2000;15(Suppl 6):67–73.
8. Apparao KB, Murray MJ, Fritz MA, Meyer WR, Chambers AF, Truong PR, et al. Osteopontin and its receptor alphavbeta(3) integrin are coexpressed in the human endometrium during the menstrual cycle but regulated differentially. J Clin Endocrinol Metab 2001;86:4991–5000.
9. Lessey BA. Adhesion molecules and implantation. J Reprod Immunol 2002; 55:101–12.
10. Ng YH, Rome S, Jalabert A, Forterre A, Singh H, Hincks CL, et al. Endometrial exosomes/microvesicles in the uterine microenvironment: a new paradigm for embryo-endometrial cross talk at implantation. PLoS One 2013;8: e58502.
11. Chen Q, Zhang Y, Elad D, Jaffa AJ, Cao Y, Ye X, et al. Navigating the site for embryo implantation: biomechanical and molecular regulation of intrauterine embryo distribution. Mol Aspects Med 2013;34:1024–42.

12. Gellersen B, Brosens JJ. Cyclic decidualization of the human endometrium in reproductive health and failure. Endocr Rev 2014;35:851–905.
13. Jensen AL, Collins J, Shipman EP, Wira CR, Guyre PM, Pioli PA. A subset of human uterine endometrial macrophages is alternatively activated. Am J Reprod Immunol 2012;68:374–86.
14. Dey SK, Lim H, Das SK, Reese J, Paria BC, Daikoku T, et al. Molecular cues to implantation. Endocr Rev 2004;25:341–73.
15. Kishimoto T, Taga T, Akira S. Cytokine signal transduction. Cell 1994;76: 253–62.
16. Ernst M, Inglese M, Waring P, Campbell IK, Bao S, Clay FJ, et al. Defective gp130-mediated signal transducer and activator of transcription (STAT) signaling results in degenerative joint disease, gastrointestinal ulceration, and failure of uterine implantation. J Exp Med 2001;194:189–203.
17. Robb L, Li R, Hartley L, Nandurkar HH, Koentgen F, Begley CG. Infertility in female mice lacking the receptor for interleukin 11 is due to a defective uterine response to implantation. Nat Med 1998;4:303–8.
18. Wang C, Umesaki N, Nakamura H, Tanaka T, Nakatani K, Sakaguchi I, et al. Expression of vascular endothelial growth factor by granulated metrial gland cells in pregnant murine uteri. Cell Tissue Res 2000;300:285–93.
19. Lee SK, Kim CJ, Kim DJ, Kang JH. Immune cells in the female reproductive tract. Immune Netw 2015;15:16–26.
20. Ying Y, Zhao GQ. Detection of multiple bone morphogenetic protein messenger ribonucleic acids and their signal transducer, Smad1, during mouse decidualization. Biol Reprod 2000;63:1781–6.
21. Paria BC, Ma W, Tan J, Raja S, Das SK, Dey SK, et al. Cellular and molecular responses of the uterus to embryo implantation can be elicited by locally applied growth factors. Proc Natl Acad Sci U S A 2001;98:1047–52.
22. Lee KY, Jeong JW, Wang J, Ma L, Martin JF, Tsai SY, et al. Bmp2 is critical for the murine uterine decidual response. Mol Cell Biol 2007;27:5468–78.
23. Sinclair DC, Mastroyannis A, Taylor HS. Leiomyoma simultaneously impair endometrial BMP-2-mediated decidualization and anticoagulant expression through secretion of TGF-beta3. J Clin Endocrinol Metab 2011;96:412–21.
24. Kuijsters NPM, Methorst WG, Kortenhorst MSQ, Rabotti C, Mischi M, Schoot BC. Uterine peristalsis and fertility: current knowledge and future perspectives: a review and meta-analysis. Reprod Biomed Online 2017; 35:50–71.
25. Dreisler E, Stampe Sorensen S, Ibsen PH, Lose G. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. Ultrasound Obstet Gynecol 2009;33:102–8.
26. Lieng M, Istre O, Sandvik L, Qvigstad E. Prevalence, 1-year regression rate, and clinical significance of asymptomatic endometrial polyps: cross-sectional study. J Minim Invasive Gynecol 2009;16:465–71.
27. Pinzauti S, Lazzeri L, Tosti C, Centini G, Orlandini C, Luisi S, et al. Transvaginal sonographic features of diffuse adenomyosis in 18-30-year-old nulligravid women without endometriosis: association with symptoms. Ultrasound Obstet Gynecol 2015;46:730–6.
28. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003;188:100–7.
29. 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.
30. 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.
31. Hinckley MD, Milki AA. 1000 office-based hysteroscopies prior to in vitro fertilization: feasibility and findings. JSLS 2004;8:103–7.
32. 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.
33. Bosteels J, Kasius J, Weyers S, Broekmans FJ, Mol BW, D'Hooghe TM. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. Cochrane Database Syst Rev 2013;1:CD009461.
34. Bosteels J, Kasius J, Weyers S, Broekmans FJ, Mol BW, D'Hooghe TM. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. Cochrane Database Syst Rev 2015:CD009461.
35. Kalampokas T, Tzanakaki D, Konidaris S, Iavazzo C, Kalampokas E, Gregoriou O. Endometrial polyps and their relationship in the pregnancy rates of patients undergoing intrauterine insemination. Clin Exp Obstet Gynecol 2012;39:299–302.
36. 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.
37. 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.
38. Pereira N, Amrane S, Estes JL, Lekovich JP, Elias RT, Chung PH, et al. Does the time interval between hysteroscopic polypectomy and start of in vitro fertilization affect outcomes? Fertil Steril 2016;105:539–44.e1.
39. Richlin SS, Ramachandran S, Shanti A, Murphy AA, Parthasarathy S. Glycodelin levels in uterine flushings and in plasma of patients with leiomyomas and polyps: implications for implantation. Hum Reprod 2002;17:2742–7.
40. Maia H Jr, Pimentel K, Silva TM, Freitas LA, Zausner B, Athayde C, et al. Aromatase and cyclooxygenase-2 expression in endometrial polyps during the menstrual cycle. Gynecol Endocrinol 2006;22:219–24.
41. Ben-Nagi J, Miell J, Yazbek J, Holland T, Jurkovic D. The effect of hysteroscopic polypectomy on the concentrations of endometrial implantation factors in uterine flushings. Reprod Biomed Online 2009;19:737–44.
42. Rackow BW, Jorgensen E, Taylor HS. Endometrial polyps affect uterine receptivity. Fertil Steril 2011;95:2690–2.
43. von Rokitansky C. Uber Uterusdrü sen-Neubildung. Z Gesellschaft Aerzte (Wien) 1860;16:577–81.
44. Meredith SM, Sanchez-Ramos L, Kaunitz AM. Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic review and metaanalysis. Am J Obstet Gynecol 2009;201:107.e1–6.
45. Champaneria R, Abedin P, Daniels J, Balogun M, Khan KS. Ultrasound scan and magnetic resonance imaging for the diagnosis of adenomyosis: systematic review comparing test accuracy. Acta Obstet Gynecol Scand 2010;89:1374–84.
46. Bazot M, Darai E. Role of transvaginal sonography and magnetic resonance imaging in the diagnosis of uterine adenomyosis. Fertil Steril 2018;109: 389–97.
47. Andres MP, Borrelli GM, Ribeiro J, Baracat EC, Abrao MS, Kho RM. Transvaginal ultrasound for the diagnosis of adenomyosis: systematic review and meta-analysis. J Minim Invasive Gynecol 2018;25:257–64.
48. Benagiano G, Habiba M, Brosens I. The pathophysiology of uterine adenomyosis: an update. Fertil Steril 2012;98:572–9.
49. Gargett CE, Schwab KE, Deane JA. Endometrial stem/progenitor cells: the first 10 years. Hum Reprod Update 2016;22:137–63.
50. Chen YJ, Li HY, Huang CH, Twu NF, Yen MS, Wang PH, et al. Oestrogen-induced epithelial-mesenchymal transition of endometrial epithelial cells contributes to the development of adenomyosis. J Pathol 2010;222: 261–70.
51. Leyendecker G, Bilgicyildirim A, Inacker M, Stalf T, Huppert P, Mall G, et al. Adenomyosis and endometriosis. Re-visiting their association and further insights into the mechanisms of auto-traumatisation. An MRI study. Arch Gynecol Obstet 2015;291:917–32.
52. Marcellin L, Santulli P, Bortolato S, Morin C, Millischer AE, Borghese B, et al. Anterior focal adenomyosis and bladder deep infiltrating endometriosis: is there a link? J Minim Invasive Gynecol 2018;25:896–901.
53. Herndon CN, Aghajanova L, Balayan S, Erikson D, Barragan F, Goldfien G, et al. Global transcriptome abnormalities of the eutopic endometrium from women with adenomyosis. Reprod Sci 2016;23:1289–303.
54. Sunkara SK, Khan KS. Adenomyosis and female fertility: a critical review of the evidence. J Obstet Gynaecol 2012;32:113–6.
55. Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. Hum Reprod 2014;29:964–77.
56. Benaglia L, Cardellicchio L, Leonardi M, Faulisi S, Vercellini P, Paffoni A, et al. Asymptomatic adenomyosis and embryo implantation in IVF cycles. Reprod Biomed Online 2014;29:606–11.

57. Benagiano G, Brosens I, Habiba M. Structural and molecular features of the endomyometrium in endometriosis and adenomyosis. Hum Reprod Update 2014;20:386–402.
58. Guo S, Li Z, Yan L, Sun Y, Feng Y. GnRH agonist improves pregnancy outcome in mice with induced adenomyosis by restoring endometrial receptivity. Drug Des Devel Ther 2018;12:1621–31.
59. Fischer CP, Kayisili U, Taylor HS. HOXA10 expression is decreased in endometrium of women with adenomyosis. Fertil Steril 2011;95:1133–6.
60. Xiao Y, Sun X, Yang X, Zhang J, Xue Q, Cai B, et al. Leukemia inhibitory factor is dysregulated in the endometrium and uterine flushing fluid of patients with adenomyosis during implantation window. Fertil Steril 2010;94:85–9.
61. Yen CF, Liao SK, Huang SJ, Tabak S, Arcuri F, Lee CL, et al. Decreased endometrial expression of leukemia inhibitory factor receptor disrupts the STAT3 signaling in adenomyosis during the implantation window. Reprod Sci 2017;24:1176–86.
62. Jiang Y, Jiang R, Cheng X, Zhang Q, Hu Y, Zhang H, et al. Decreased expression of NR4A nuclear receptors in adenomyosis impairs endometrial decidualization. Mol Hum Reprod 2016;22:655–68.
63. Carrarelli P, Yen CF, Funghi L, Arcuri F, Tosti C, Bifulco G, et al. Expression of inflammatory and neurogenic mediators in adenomyosis. Reprod Sci 2017;24:369–75.
64. Tremellen KP, Russell P. The distribution of immune cells and macrophages in the endometrium of women with recurrent reproductive failure. II: adenomyosis and macrophages. J Reprod Immunol 2012;93:58–63.
65. Zhihong N, Yun F, Pinggui Z, Sulian Z, Zhang A. Cytokine profiling in the eutopic endometrium of adenomyosis during the implantation window after ovarian stimulation. Reprod Sci 2016;23:124–33.
66. Feng T, Wei S, Wang Y, Fu X, Shi L, Qu L, et al. Rhein ameliorates adenomyosis by inhibiting NF-kappaB and beta-Catenin signaling pathway. Biomed Pharmacother 2017;94:231–7.
67. Lai TH, Chang FW, Lin JJ, Ling QD. Endometrial L-selectin ligand is downregulated in the mid-secretory phase during the menstrual cycle in women with adenomyosis. Taiwan J Obstet Gynecol 2018;57:507–16.
68. Xiao Y, Li T, Xia E, Yang X, Sun X, Zhou Y. Expression of integrin beta3 and osteopontin in the eutopic endometrium of adenomyosis during the implantation window. Eur J Obstet Gynecol Reprod Biol 2013;170:419–22.
69. Streuli I, Santulli P, Chouzenoux S, Chapron C, Batteux F. Serum osteopontin levels are decreased in focal adenomyosis. Reprod Sci 2017;24:773–82.
70. Kitawaki J, Koshiba H, Ishihara H, Kusuki I, Tsukamoto K, Honjo H. Progesterone induction of 17beta-hydroxysteroid dehydrogenase type 2 during the secretory phase occurs in the endometrium of estrogen-dependent benign diseases but not in normal endometrium. J Clin Endocrinol Metab 2000;85:3292–6.
71. Jichan N, Xishi L, Guo SW. Promoter hypermethylation of progesterone receptor isoform B (PR-B) in adenomyosis and its rectification by a histone deacetylase inhibitor and a demethylation agent. Reprod Sci 2010;17:995–1005.
72. Nie J, Lu Y, Liu X, Guo SW. Immunoreactivity of progesterone receptor isoform B, nuclear factor kappaB, and IkappaBalpha in adenomyosis. Fertil Steril 2009;92:886–9.
73. Jiang JF, Sun AJ, Xue W, Deng Y, Wang YF. Aberrantly expressed long noncoding RNAs in the eutopic endometria of patients with uterine adenomyosis. Eur J Obstet Gynecol Reprod Biol 2016;199:32–7.
74. Liu X, Guo SW. Aberrant immunoreactivity of deoxyribonucleic acid methyltransferases in adenomyosis. Gynecol Obstet Invest 2012;74:100–8.
75. Kissler S, Hamscho N, Zangos S, Wiegratz I, Schlichter S, Menzel C, et al. Uterotubal transport disorder in adenomyosis and endometriosis—a cause for infertility. BJOG 2006;113:902–8.
76. Ijland MM, Evers JL, Dunselman GA, Volovics L, Hoogland HJ. Relation between endometrial wavelike activity and fecundability in spontaneous cycles. Fertil Steril 1997;67:492–6.
77. Fanchin R, Righini C, Olivennes F, Taylor S, de Ziegler D, Frydman R. Uterine contractions at the time of embryo transfer alter pregnancy rates after in-vitro fertilization. Hum Reprod 1998;13:1968–74.
78. Zhu L, Li Y, Xu A. Influence of controlled ovarian hyperstimulation on uterine peristalsis in infertile women. Hum Reprod 2012;27:2684–9.
79. Zhu L, Che HS, Xiao L, Li YP. Uterine peristalsis before embryo transfer affects the chance of clinical pregnancy in fresh and frozen-thawed embryo transfer cycles. Hum Reprod 2014;29:1238–43.
80. Zhu L, Xiao L, Che HS, Li YP, Liao JT. Uterine peristalsis exerts control over fluid migration after mock embryo transfer. Hum Reprod 2014;29:279–85.
81. Rizner TL. The important roles of steroid sulfatase and sulfotransferases in gynecological diseases. Front Pharmacol 2016;7:30.
82. Niu Z, Chen Q, Sun Y, Feng Y. Long-term pituitary downregulation before frozen embryo transfer could improve pregnancy outcomes in women with adenomyosis. Gynecol Endocrinol 2013;29:1026–30.
83. Park CW, Choi MH, Yang KM, Song IO. Pregnancy rate in women with adenomyosis undergoing fresh or frozen embryo transfer cycles following gonadotropin-releasing hormone agonist treatment. Clin Exp Reprod Med 2016;43:169–73.
84. Khan KN, Kitajima M, Hiraki K, Fujishita A, Sekine I, Ishimaru T, et al. Changes in tissue inflammation, angiogenesis and apoptosis in endometriosis, adenomyosis and uterine myoma after GnRH agonist therapy. Hum Reprod 2010;25:642–53.
85. Zhou CY, Xu XJ, He J. [Pregnancy outcomes and symptom improvement of patients with adenomyosis treated with high intensity focused ultrasound ablation]. Zhonghua Fu Chan Ke Za Zhi 2016;51:845–9.
86. Zhang L, Rao F, Setzen R. High intensity focused ultrasound for the treatment of adenomyosis: selection criteria, efficacy, safety and fertility. Acta Obstet Gynecol Scand 2017;96:707–14.
87. Dueholm M. Uterine adenomyosis and infertility, review of reproductive outcome after in vitro fertilization and surgery. Acta Obstet Gynecol Scand 2017;96:715–26.
88. Oliveira MAP, Crispi CP Jr, Brollo LC, Crispi CP, De Wilde RL. Surgery in adenomyosis. Arch Gynecol Obstet 2018;297:581–9.
89. Tan J, Moriarty S, Taskin O, Allaire C, Williams C, Yong P, et al. Reproductive outcomes after fertility-sparing surgery for focal and diffuse adenomyosis: a systematic review. J Minim Invasive Gynecol 2018;25:608–21.
90. Younes G, Tulandi T. Conservative surgery for adenomyosis and results: a systematic review. J Minim Invasive Gynecol 2018;25:265–76.
91. Bulun SE. Uterine fibroids. N Engl J Med 2013;369:1344–55.
92. Mas A, Cervello I, Fernandez-Alvarez A, Faus A, Diaz A, Burgues O, et al. Overexpression of the truncated form of High Mobility Group A proteins (HMGA2) in human myometrial cells induces leiomyoma-like tissue formation. Mol Hum Reprod 2015;21:330–8.
93. Yin P, Ono M, Moravek MB, Coon JS 5th, Navarro A, Monsivais D, et al. Human uterine leiomyoma stem/progenitor cells expressing CD34 and CD49b initiate tumors in vivo. J Clin Endocrinol Metab 2015;100:E601–6.
94. Yang Q, Diamond MP, Al-Hendy A. Early life adverse environmental exposures increase the risk of uterine fibroid development: role of epigenetic regulation. Front Pharmacol 2016;7:40.
95. Katz TA, Yang Q, Trevino LS, Walker CL, Al-Hendy A. Endocrine-disrupting chemicals and uterine fibroids. Fertil Steril 2016;106:967–77.
96. Yang Q, Diamond MP, Al-Hendy A. Converting of myometrial stem cells to tumor-initiating cells: mechanism of uterine fibroid development. Cell Stem Cells Regen Med 2016;2.
97. Mas A, Stone L, O'Connor PM, Yang Q, Kleven D, Simon C, et al. Developmental exposure to endocrine disruptors expands murine myometrial stem cell compartment as a prerequisite to leiomyoma tumorigenesis. Stem Cells 2017;35:666–78.
98. Andersen J, DyReyes VM, Barbieri RL, Coachman DM, Miksicek RJ. Leiomyoma primary cultures have elevated transcriptional response to estrogen compared with autologous myometrial cultures. J Soc Gynecol Invest 1995;2:542–51.
99. Pedeutour F, Quade BJ, Weremowicz S, Dal Cin P, Ali S, Morton CC. Localization and expression of the human estrogen receptor beta gene in uterine leiomyomata. Genes Chromosomes Cancer 1998;23:361–6.
100. Bulun SE, Simpson ER, Word RA. Expression of the CYP19 gene and its product aromatase cytochrome P450 in human uterine leiomyoma tissues and cells in culture. J Clin Endocrinol Metab 1994;78:736–43.
101. Arici A, Sozen I. Transforming growth factor-beta3 is expressed at high levels in leiomyoma where it stimulates fibronectin expression and cell proliferation. Fertil Steril 2000;73:1006–11.

102. Tanwar PS, Lee HJ, Zhang L, Zukerberg LR, Taketo MM, Rueda BR, et al. Constitutive activation of Beta-catenin in uterine stroma and smooth muscle leads to the development of mesenchymal tumors in mice. Biol Reprod 2009;81:545–52.
103. Doherty LF, Taylor HS. Leiomyoma-derived transforming growth factor-beta impairs bone morphogenetic protein-2-mediated endometrial receptivity. Fertil Steril 2015;103:845–52.
104. Klatsky PC, Tran ND, Caughey AB, Fujimoto VY. Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. Am J Obstet Gynecol 2008;198:357–66.
105. Eldar-Geva T, Meagher S, Healy DL, MacLachlan V, Breheny S, Wood C. Effect of intramural, subserosal, and submucosal uterine fibroids on the outcome of assisted reproductive technology treatment. Fertil Steril 1998;70:687–91.
106. Casini ML, Rossi F, Agostini R, Unfer V. Effects of the position of fibroids on fertility. Gynecol Endocrinol 2006;22:106–9.
107. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009;91:1215–23.
108. Christopoulos G, Vlismas A, Salim R, Islam R, Trew G, Lavery S. Fibroids that do not distort the uterine cavity and IVF success rates: an observational study using extensive matching criteria. BJOG 2017;124:615–21.
109. Styer AK, Jin S, Liu D, Wang B, Polotsky AJ, Christianson MS, et al. Association of uterine fibroids and pregnancy outcomes after ovarian stimulation-intrauterine insemination for unexplained infertility. Fertil Steril 2017;107:756–62.e3.
110. Klatsky PC, Lane DE, Ryan IP, Fujimoto VY. The effect of fibroids without cavity involvement on ART outcomes independent of ovarian age. Hum Reprod 2007;22:521–6.
111. Hasegawa E, Ito H, Hasegawa F, Hatano K, Kazuka M, Usuda S, et al. Expression of leukemia inhibitory factor in the endometrium in abnormal uterine cavities during the implantation window. Fertil Steril 2012;97:953–8.
112. Hambartsoumian E. Endometrial leukemia inhibitory factor (LIF) as a possible cause of unexplained infertility and multiple failures of implantation. Am J Reprod Immunol 1998;39:137–43.
113. Munro MG, Critchley HO, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet 2011;113:3–13.
114. Munro MG, Critchley HOD, Fraser IS, FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynaecol Obstet 2018;143:393–408.
115. Healy DL. Impact of uterine fibroids on ART outcome. Environ Health Perspect 2000;108(Suppl 5):845–7.
116. Hart R, Khalaf Y, Yeong CT, Seed P, Taylor A, Braude P. A prospective controlled study of the effect of intramural uterine fibroids on the outcome of assisted conception. Hum Reprod 2001;16:2411–7.
117. Khalaf Y, Ross C, El-Toukhy T, Hart R, Seed P, Braude P. The effect of small intramural uterine fibroids on the cumulative outcome of assisted conception. Hum Reprod 2006;21:2640–4.
118. Guven S, Kart C, Unsal MA, Odaci E. Intramural leoimyoma without endometrial cavity distortion may negatively affect the ICSI - ET outcome. Reprod Biol Endocrinol 2013;11:102.
119. Sunkara SK, Khairy M, El-Toukhy T, Khalaf Y, Coomarasamy A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum Reprod 2010;25:418–29.
120. Metwally M, Farquhar CM, Li TC. Is another meta-analysis on the effects of intramural fibroids on reproductive outcomes needed? Reprod Biomed Online 2011;23:2–14.
121. Farhi J, Ashkenazi J, Feldberg D, Dicker D, Orvieto R, Ben Rafael Z. Effect of uterine leiomyomata on the results of in-vitro fertilization treatment. Hum Reprod 1995;10:2576–8.
122. Surrey ES, Lietz AK, Schoolcraft WB. Impact of intramural leiomyomata in patients with a normal endometrial cavity on in vitro fertilization-embryo transfer cycle outcome. Fertil Steril 2001;75:405–10.
123. Yarali H, Bukulmez O. The effect of intramural and subserous uterine fibroids on implantation and clinical pregnancy rates in patients having intracytoplasmic sperm injection. Arch Gynecol Obstet 2002;266:30–3.
124. Oliveira FG, Abdelmassih VG, Diamond MP, Dozortsev D, Melo NR, Abdelmassih R. Impact of subserosal and intramural uterine fibroids that do not distort the endometrial cavity on the outcome of in vitro fertilization-intracytoplasmic sperm injection. Fertil Steril 2004;81:582–7.
125. Yan L, Ding L, Li C, Wang Y, Tang R, Chen ZJ. Effect of fibroids not distorting the endometrial cavity on the outcome of in vitro fertilization treatment: a retrospective cohort study. Fertil Steril 2014;101:716–21.
126. Makker A, Goel MM, Nigam D, Bhatia V, Mahdi AA, Das V, et al. Endometrial expression of homeobox genes and cell adhesion molecules in infertile women with intramural fibroids during window of implantation. Reprod Sci 2017;24:435–44.
127. Horcajadas JA, Goyri E, Higon MA, Martinez-Conejero JA, Gambadauro P, Garcia G, et al. Endometrial receptivity and implantation are not affected by the presence of uterine intramural leiomyomas: a clinical and functional genomics analysis. J Clin Endocrinol Metab 2008;93:3490–8.
128. Aghajanova L, Houshdaran S, Irwin JC, Giudice LC. Effects of noncavity-distorting fibroids on endometrial gene expression and function. Biol Reprod 2017;97:564–76.
129. Yan L, Yu Q, Zhang YN, Guo Z, Li Z, Niu J, et al. Effect of type 3 intramural fibroids on in vitro fertilization-intracytoplasmic sperm injection outcomes: a retrospective cohort study. Fertil Steril 2018;109:817–22.e2.
130. Rogers R, Norian J, Malik M, Christman G, Abu-Asab M, Chen F, et al. Mechanical homeostasis is altered in uterine leiomyoma. Am J Obstet Gynecol 2008;198:474.e1–11.
131. Payson M, Malik M, Siti-Nur Morris S, Segars JH, Chason R, Catherino WH. Activating transcription factor 3 gene expression suggests that tissue stress plays a role in leiomyoma development. Fertil Steril 2009;92:748–55.
132. Norian JM, Owen CM, Taboas J, Korecki C, Tuan R, Malik M, et al. Characterization of tissue biomechanics and mechanical signaling in uterine leiomyoma. Matrix Biol 2012;31:57–65.
133. Orisaka M, Kurokawa T, Shukunami K, Orisaka S, Fukuda MT, Shinagawa A, et al. A comparison of uterine peristalsis in women with normal uteri and uterine leiomyoma by cine magnetic resonance imaging. Eur J Obstet Gynecol Reprod Biol 2007;135:111–5.
134. Yoshino O, Hayashi T, Osuga Y, Orisaka M, Asada H, Okuda S, et al. Decreased pregnancy rate is linked to abnormal uterine peristalsis caused by intramural fibroids. Hum Reprod 2010;25:2475–9.
135. Shokeir T, El-Shafei M, Yousef H, Allam AF, Sadek E. Submucous myomas and their implications in the pregnancy rates of patients with otherwise unexplained primary infertility undergoing hysteroscopic myomectomy: a randomized matched control study. Fertil Steril 2010;94:724–9.
136. Unlu C, Celik O, Celik N, Otlu B. Expression of endometrial receptivity genes increase after myomectomy of intramural leiomyomas not distorting the endometrial cavity. Reprod Sci 2016;23:31–41.
137. Berman JM, Thiel J, Brucker SY. Reproductive outcomes in subjects following radiofrequency volumetric thermal ablation (RFVTA) of their symptomatic myomas: a retrospective case series. J Minim Invasive Gynecol 2015;22:S237.
138. Keltz J, Levie M, Chudnoff S. Pregnancy outcomes after direct uterine myoma thermal ablation: review of the literature. J Minim Invasive Gynecol 2017;24:538–45.
139. Rabinovici J, David M, Fukunishi H, Morita Y, Gostout BS, Stewart EA, et al. Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. Fertil Steril 2010;93:199–209.
140. Torre A, Paillusson B, Fain V, Labauge P, Pelage JP, Fauconnier A. Uterine artery embolization for severe symptomatic fibroids: effects on fertility and symptoms. Hum Reprod 2014;29:490–501.
141. Torre A, Fauconnier A, Kahn V, Limot O, Bussierres L, Pelage JP. Fertility after uterine artery embolization for symptomatic multiple fibroids with no other infertility factors. Eur Radiol 2017;27:2850–9.