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Surgery for Benign Gynecological Disorders Improve Endometrium Receptivity: A Systematic Review of the Literature

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Abstract

Regardless of the anatomical locations, some benign gynecological disorders (BGDs) such as peritoneal endometriosis, ovarian endometrioma, adenomyosis, uterine leiomyomas, endometrial polyps, uterine septum, and hydrosalpinges may lead to implantation failure. Despite progress in medical therapies, surgery remains a mainstay of BGDs treatment. Although our knowledge of endometrial receptivity after BGDs surgery is limited, it has allowed for significant improvement in the treatment of female subfertility. Many researchers studied on pregnancy outcome following BGDs surgery, but they did not investigate the possible impact of surgery on endometrial receptivity. They, therefore, concluded that pregnancy rates improved after BGDs surgery based on clinical observations. Many of these clinicians believe that surgical resection of BGDs leads to removal of local mechanical effect over the endometrium. Moreover, they accept that BGDs surgery may inhibit the detrimental signaling and secretion of some molecules from the BGDSs into the endometrium that may lead to favorable effect on the endometrium. However, so far, data from randomized controlled trials or systematic review or meta-analyses to answer the question whether surgical treatment of BGDs can improve endometrial receptivity are lacking. The purpose of this systematic review was to evaluate the results of available publications dealing with the impact of reproductive surgery for BGDs on endometrial receptivity.

Keywords

benign gynecological disorders, surgery, endometrium, receptivity

Introduction

Defects in endometrial receptivity that contribute to subfertility have been linked to a wide range of benign gynecological disorders (BGDs), all of which can impair successful implantation.[1,2] Studies have revealed differences in the expression of several genes and inflammatory cytokines in eutopic endometrium of women with BGDs.[3-6] Regardless of the anatomical location, some benign lesions such as peritoneal endometriosis, ovarian endometriomas, adenomyosis, uterine leiomyomas, endometrial polyps, uterine septum, and hydrosalpinges might be associated with implantation failure, leading to disturbed receptivity and pathological inflammation in the endometrium.[3,4,7-10] Direct contact between the endometrium and the solid and/or cystic BGDs are not mandatory to negatively influence the endometrium receptivity. Recent study has reported that isolated peritoneal endometriotic implants influence the pregnancy rate independent of their location and implant size.[11] Therefore, BGDs located along the peritoneum–ovary–myometrium–endometrium axis might affect the endometrial

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receptivity independent of their location.[3,5,7-10] Benign gynecological disorders-associated infertility is not exclusively due to mechanical factors, defective folliculogenesis, and reduced fertilization but also the result of defective implantation capacity.[5,12] Although endometrial receptivity of some patients having endometriosis, uterine septum, and nonendometriotic benign ovarian cysts might not be altered during the window of implantation, the underlying mechanisms of BGDs-associated subfertility remain elusive.[7,13]

Assessment of the endometrium in women with BGDs-associated subfertility showed an abnormal expression of putative implantation markers such as homeobox (HOX) genes, αvβ3 integrins, and leukemia inhibitory factor (LIF).[3,4,14,15] As an example, the presence of hydrosalpinx reduces the receptivity of the endometrium by decreasing the expression of LIF and HOX genes.[16,17] Likewise, it has been reported that ovarian endometrioma increases nuclear factor κB (NF-κB)-related pathological endometrial inflammation.[3] Further, glandular endometrial atrophy is the most frequently noted histological finding secondary to uterine leiomyomas.[18] Differences in the expression of some receptivity molecules suggest that the endometrium of women with BGDs may appear histologically normal but, in fact, be genetically abnormal. Together, we can propose that BGDs may affect the endometrial receptivity through a specific and selective molecular and genetic mechanisms.

Despite progress in medical therapies, surgery remains a mainstay of BGDs treatment. Several drawbacks of the current BGDs treatment with medical agents often lead to abandonment of nonsurgical approaches and repeated surgical therapy. So far, the availability of nonsurgical approaches has failed to substantially change everyday clinical practice, and the majority of women with endometrioma, symptomatic uterine fibroids, and deep peritoneal endometriosis are still managed surgically. This is, at least partly, because some of the medical agents are still investigational, which poses the problem of their long-term safety and efficacy compared to standard surgical treatment. In connection with all medications currently available for endometrioma/endometriosis, adenomyosis or fibroid treatment including GnRH agonist, ovarian steroids, progesterone receptor antagonist, and selective progesterone receptor modulator are unsuitable for long-term use because of their significant side effects.[19]

The data to date suggest that surgical approaches hold promise for improved fertility outcome for appropriately selected infertile women with endometriomas or symptomatic uterine leiomyomas but still are too few to draw conclusions about the impact of surgery on endometrium receptivity.[3,4,7] Many researchers studied on pregnancy outcome after BGDs surgery, but they did not investigate the impact of surgery on endometrial receptivity. They, therefore, concluded that pregnancy rates increased after BGDs surgery based on clinical observations. Many of these clinicians believe that surgical resection of BGDs leads to removal of local mechanical effect over the endometrium.[1,2] Moreover, they accept that BGDs surgery may inhibit the detrimental signaling and secretion of some molecules from the BGDs into the endometrium, which may lead to favorable effect on the endometrium.[1-4] However, so far data from randomized controlled trials or systematic review or meta-analyses to answer the question whether surgical treatment of BGDs can improve endometrial receptivity are lacking.

The purpose of this systematic review was to evaluate the results of available publications dealing with the impact of reproductive tissue surgery for BGDs on endometrial receptivity. Due to difficulties in obtaining and evaluating endometrial tissue samples in humans, we have included the experimental studies investigating endometrium receptivity in BGD models to discuss what mechanisms are associated with the disturbance of endometrial receptivity in different species. Studies evaluating possible impacts of medical treatment of BGDs on endometrial receptivity was also included in the review. Before review of the literature, we will try to give some information about endometrium characteristics, nonsurgical treatment options, and animal models of BGDs.

Endometrium Characteristics of BGDs

The endometrium is accepted as a final destination allowing blastocyst to attach under sufficient amounts of biologically relevant receptivity molecules.[20] Disturbed expression of the receptivity genes and molecules in the endometrium during the window of implantation might be a common factor among patients with infertility due to different benign gynecological etiologies. In good agreement, endometrial receptivity defects have been noted in a variety of clinical disorders, including hydrosalpinges, endometriosis, endometrioma, endometrial polyp, uterine leiomyoma, and polycystic ovary syndrome.[1,4] Discordantly, many animal species having infertility do not exhibit histological evidence of defective endometrium. For instance, endometrium of HOXA10-deficient mice shows normal histological appearance.[21]

There are 2 types of endometrial receptivity defects. Each of them might be seen in different form of BGDs. In type I defect, the lack of the integrin β3 subunit leads to delayed expression of αvβ3 integrin. Cases with out-of-phase endometrium show type I endometrial defect. Type II is the occult form of endometrial receptivity defect and leads to decreased implantation rates.[14] Endometrium in the type II defect is histological in phase and normal in appearance. However, expression of the endometrial αvβ3 integrin decreased. Endometriosis is likely the most common cause of endometrial receptivity defects, especially in cases of minimal or mild disease for which mechanical reasons do not explain the loss of fertility. Concordantly, type II endometrial receptivity defect has been reported in the endometrium of women with minimal and mild endometriosis and the endometrium of unexplained infertility.[14,22] In good agreement, administration of peritoneal fluid from women with endometriosis to mice not only reduces expression of LIF and αvβ3 integrin but also leads to decline in HOXA-10 expression.[23] It is most likely that inflammatory contents of peritoneal fluid may negatively affect endometrial

Table 1. Endometrium Characteristics of Different BGDs.

BGD	Endometrium Characteristics
Endometriosis/ endometrioma	• Upregulation of ER and absence of PRb,[25,26] • ⇧NF-κB, Bcl-2 expression • ⇧nerve fiber density • ⇩HOXA-10, αvβ3 integrin expression • ⇩apoptosis • defective aromatase metabolism[3,14,27-30] • ⇧endometrial polyp[31] • ⇩lymphocyte-mediated cytotoxicity[32] • ⇩natural killer cell activity[32]
Adenomyosis	• 27%-70% of women with endometriosis concomitantly had adenomyosis[33,34] • ⇧angiogenesis • ⇩decreased apoptosis • progesterone resistance • defective cytokine expression[35] • ⇩LIF and IL-11expression[36]
Leiomyoma	• Glandular endometrial atrophy[18] • BMP-2 resistance[37-39] • Fibroid derived TGF-β3 induces BMP-2 resistance and leads to defective decidualization[37]
Hydrosalpinx	• Defective αvβ3, HOXA-10, and LIF expression[8,16,17] • Reflux of alkaline hydrosalpinx content disturbs receptivity[40,41]
Endometrial polyp	• Failed expression of endometrial IGFBP-1, glycodelin, TNF-α, and osteopontin[10,42] • ⇧expression of endometrial NF-κB1[43]
Uterine septum	• Endometrium of women with uterine septum is similar to the endometrium of fertile participants[7]
Nonendometriotic benign ovarian cyst	• Endometrium of women having serous, dermoid, and mucinous ovarian cysts are similar to the endometrium of fertile participants[3,4]

Abbreviations: NF-κB, nuclear factor κB; ER, estrogen receptor; PRb, progesterone receptor b; HOXA-10, homeobox A10; LIF, leukemia inhibitory factor; IL-11, interleukin 11; TNF-α, tumor necrosis factor α.

receptivity by inhibiting expression of some specific endometrial proteins including αvβ3 integrin [24] (Table 1).

Endometrium Characteristics in Endometriosis/ Endometrioma

Eutopic endometrium of women with endometriosis is different from that of women without endometriosis. Attenuated progesterone response in endometrium from women with endometriosis has been reported.[44] In addition, increased NF-κB, Bcl-2 expression, increased nerve fiber density, decreased endometrial HOXA-10, αvβ3 integrin expression and apoptosis, defective aromatase, and estrogen metabolism have been reported in the endometrial cells of women with endometriosis.[3,14,27-30] Another defect observed in eutopic endometrium of women with endometriosis is the failed expression pattern of estrogen receptors (ER) and progesterone receptors (PR). It is a well-known fact that an increase in progesterone relative to estrogen is required for successful implantation. Although ER is down-regulated at the time of implantation in fertile participants, women having endometriosis, however, were reported to have an upregulation of ER and absence of PRb.[25,26] Therefore, some receptivity genes induced by progesterone such as HOXA10 and HOXA11 were dysregulated in the endometrium of women with endometriosis.[15] These data support the idea that eutopic endometrium may have a critical role in endometriosis-related subfertility.[45]

In terms of endometrial receptivity markers, both HOXA-10 and αvβ3 expressions have been shown to be significantly reduced in the endometrium of women with mild but not moderate or severe endometriosis.[14,46] Concordantly, studies have demonstrated that the presence of endometriosis might induce aberrant methylation of HOX genes in the eutopic endometrium.[24,47] Wu et al demonstrated that HOXA-10 was hypermethylated in the endometrium of women with endometriosis.[48]

Increased prevalance of endometrial polyp in women with endometriosis may also support the possible interaction between endometriotic lesions and defective endometrium. In good agreement, recent meta-analysis reported that the incidence of endometrial polyp in women with endometriosis significantly increased.[31] The risk of endometrial polyp was found to be increased in patients at stages 2 to 4 when compared to those at stage 1.[31] Likewise, decreased lymphocyte-mediated cytotoxicity and natural killer cell activity within the endometrium of women with endometriosis have been reported.[32]

Endometrium Characteristics in Uterine Leiomyomas

Endometrium of women with uterine leiomyomas may appear histologically normal but, in fact, may show molecular abnormality.[7] It is likely that defective regulation of some growth factors and cytokines inside the endometrial cells of women with uterine leiomyomas may be responsible for damaged endometrial receptivity.[48,31] Harmful signaling molecules that originate from the intramural leiomyomas may reach the endometrium via intercellular communication routes and may lead to negative endometrial effects. Concordantly, it has been reported that glandular endometrial atrophy is the most frequently noted histological finding secondary to uterine leiomyomas.[18] Moreover, uterine leiomyomas secrete great amount of transforming growth factor β3 (TGF-β3) and endometrium of women having uterine leiomyomas show bone morphogenetic protein 2 (BMP-2) resistance.[37-39] Taken together, TGF-β3 secretion from uterine leiomyomas induces BMP-2 resistance in endometrium and leads to defective endometrial decidualization.[37]

Endometrium Characteristics in Adenomyosis

The association between adenomyosis and subfertility has been reported.[49] Accumulating data have demonstrated that there is

a close association between the occurrence of adenomyosis and functional defects in eutopic endometrium. Adenomyosis reduces endometrial receptivity in a manner similar to endometriosis. Concordantly, it has been reported that 27% to 70% of women with endometriosis concomitantly had adenomyosis,[33,34] and the latter is associated with lifelong infertility in a baboon model of adenomyosis.[50] Similar to eutopic endometrium of patients with endometriosis, endometrium of cases with adenomyosis exhibits increased angiogenesis, decreased apoptosis, local estrogen synthesis, progesterone resistance, and defective cytokine expression.[35] Alike, Yen et al have reported that some implantation markers including LIF and interleukin (IL) 11 are decreased in the endometrium of women with adenomyosis.[36]

Endometrium Characteristics in Hydrosalpinges

Both unilateral and bilateral hydrosalpinges as well as tubal phimosis may negatively affect endometrium receptivity.[51,52] Hydrosalpinx fluid consists of some cytokines, prostaglandins, and inflammatory substances. Reflux of alkaline hydrosalpinx content into the endometrial cavity might disturb endometrium receptivity. In addition, hydrosalpinx fluid may negatively affect endometrial apposition and attachment of blastocyst.[8,40,41] In good agreement, defective expression of $\alpha v\beta 3$, HOXA-10, and LIF genes were noted during the midsecretory phase in endometrium of patients with hydrosalpinges.[8,16,17]

Endometrium Characteristics in Uterine Septum and Endometrial Polyps

Uterine septum and endometrial polyps not only lead to mechanical interference with sperm and embryo but may also alter endometrial receptivity and implantation. Failed expression of endometrial insulin-like growth factor 1 binding protein (IGFBP-1), glycodelin, tumor necrosis factor α (TNF-α), and osteopontin have been reported in women with endometrial polyp.[10,42] Conversely, increased expression of endometrial NF-κB1, an inflammatory marker, has been reported in women having endometrial polyps, suggesting pathological endometrial inflammation.[43]

It is plausible that uterine septum may adversely affect the endometrium and impair endometrial receptivity. However, there is no comprehensive study investigating the endometrial histology and receptivity markers in women with uterine septum. Therefore, little is known how uterine septum leads to infertility. Concordantly, in a recent study, our group demonstrated that there was no significant change in the endometrium of women with uterine septum compared to fertile controls.[7]

Nonsurgical/Medical Therapy of BGDs

The currently available data on pregnancy after nonsurgical approaches (medical treatment or minimally invasive procedures) are insufficient to routinely offer medical treatment as an alternative to myomectomy or endometrioma resection to women who wish to preserve, or enhance, their fertility. Another unresolved issue with medical approaches for leiomyomas, adenomyosis, and endometriomas concern the durability of clinical improvement over time. If endometrioma, adenomyosis, or fibroid tissues are not removed, patients receiving medical treatment might be at risk of regrowth of the remaining issues. However, in women having very large or difficult-to-remove fibroids or endometrioma, or in whom surgery is contraindicated, nonsurgical approaches may be preferred.

Combined oral contraceptives, progesterones, GnRH analogs, or aromatase inhibitors can be used in treatment of some BGDs to prevent estrogen synthesis or block its action.[38] However, there is little evidence to support use of medical agents in women with endometriosis who wish to improve fertility.[53] Hence, last decade studies investigating possible impact of medical treatment of endometriosis has turned toward TNF-α, macrophage migration inhibitory factor, prostoglandin E2, and estrogen receptor β pathways as potential targets for treatment of endometriosis. Experimental studies investigating these pathways have provided promising results on their ability to suppress implant growth.[54-57] Unfortunately, confirmatory studies in human participants remain to be initiated.

The main problem limiting the use of medical treatment of endometriosis is the existence of PR resistance. Decreased PR-A and increased ratio of PR-B to PR-A were reported in the eutopic endometrium of endometriosis and adenomyosis.[35,58] The altered PR expression may lead to decreased expression of progesterone-responsive mediators including HOX genes.[15] Concordantly, in baboons with induced endometriosis, endometrial HOXA expression was found to be downregulated.[35] Likewise, defective PR expression seen in endometriosis and adenomyosis may be related to the poor response of both diseases to progestational agents.[59] Collectively, progesterone resistance may lead to defective endometrial receptivity and medical treatment failures in endometriosis and adenomyosis.

Due to the small sample size, most studies lack sufficient power to appropriately assess the relative impact of the medical treatment on endometrium receptivity. Likewise, there is no option of medical treatment for endometrial polyp, hydrosalpinges, and uterine septum. Together, as the total number of cases treated by medical agents are quite small when compared to myomectomy or endometrioma resection, it is difficult to draw conclusion about the relative pros and cons of nonsurgical approaches for BGDs.

Animal Models of BGDs

As endometrium receptivity is complex and difficult to obtain and evaluates endometrial tissue in humans, we and others have looked into animal models to study endometrium receptivity. Although murine models for leiomyomas have been reported, uterine leiomyomas are rare in animals, and there is no universally accepted animal model. Although some species of rats may develop tumors that resemble uterine leiomyomas, the

growth patterns of these tumors do not display the characteristic features of the human leiomyomas.[60] Likewise, there is no universally accepted animal model for endometrial polyp, uterine septum, and hydrosalpinges.

It is difficult to evaluate the impact of adenomyosis on endometrium receptivity as the final diagnosis required hysterectomy. Likewise, the uncertain and multiple etiologies of endometriosis and the need for laparoscopy to diagnose meant that many cases remained undetected and limited our understanding of their relation to receptivity. Due to these facts, the generation of animal model of endometriosis and adenomyosis can have important implications on our understanding of the etiology of both diseases. The diagnostic difficulties regarding both diseases have led to the development of different experimental models for adenomyosis and endometriosis, which include baboons, rodents, and immunocompromised nude mice.[61-63] Cycle characteristics and anatomy of the reproductive organs are very similar in both women and baboons.[64] Therefore, baboon widely is used as a model for the study of some BGDs in humans.[65] Results obtained from experimental studies clearly demonstrated that the rodent and baboon models are potential tools to study the pathophysiology and pathogenesis of endometriosis and adenomyosis, respectively, in women.[62] However, Dehoux and colleagues performed a study that questioned the appropriateness of the baboon model for endometriosis research.[66] They have reported that baboons have effective mechanisms to cleanse and renew their peritoneum after induction of endometriosis, limiting the reliability of results. Hence, there is a doubt whether the baboon is a relevant model for endometriosis researches.[66] Further, researches investigating endometrium receptivity in animal experiments is not necessarily transposable to the human model of implantation.

Methods

Search Strategy

A systematic review of the available evidence was performed to assess the efficacy of surgery on endometrium receptivity as a treatment of BGDs. We carefully searched PubMed for relevant studies available online and published between 1990 and 2015. The last retrieval date was December 31, 2015. Studies not published in English were excluded. PubMed database was searched for studies that explored the efficacy of BGDs surgery on endometrial receptivity in women with ovarian endometriomas, peritoneal endometriosis, uterine leiomyomas, adenomyosis, uterine septum, endometrial polyps, and hydrosalpinges. The search terms "endometrioma/endometriosis resection/removal/cystectomy/ablation and endometrium/receptivity" or "myomectomy (laparoscopy/laparotomy) and endometrium/receptivity" or "adenomyosis surgery/resection/removal and endometrium/receptivity" or "hysteroscopic polypectomy and endometrium/receptivity" or "metroplasty/septum resection, and endometrium/receptivity" or "salpingectomy, hydrosalpinges removal, and endometrium/receptivity" were used as key words. Primarily, HOX gene, a well-known endometrial receptivity marker, was written into the PubMed search box to identify endometrial receptivity. During database search for HOX genes, detection of studies investigating other receptivity markers, growth factors, and cytokines were also included in the review. Exclusion of these markers would have led to missing out important data and available evidence. These subsets were combined using "AND" to generate final citations addressing the research question. The reference list of all published receptivity trials including review articles were examined to identify articles not noted by the electronic search of the PubMed.

Selection of Articles

Five reviewers (M.A., E.T.H., T.A. M.B., L.S., F.F.V.) independently assessed all studies for inclusion or exclusion. Any disagreement was resolved in discussion with the other authors (O.C., T.K., and E.C). The references of the selected articles were also checked for possible endometrial receptivity studies to include. Due to lack of randomized controlled studies investigating endometrium receptivity following surgery, the included studies in the review were prospective nonrandomized, where women with BGDs had undergone surgical removal of the lesions and obtained endometrial samples. The nonrandomized receptivity studies were vigorously reviewed and good quality prospective or case controlled trials that met all predefined criteria were included. The studies were excluded if they were a retrospective trial. Case series, reviews, comments, letters, and editorials were also excluded. At the first screening, manuscript titles were investigated, and studies with lack of any relevance were excluded. Articles evaluating endometrial receptivity in experimental models were included, but their conclusions were made separately. Likewise, articles evaluating the impact of nonsurgical approaches on endometrial receptivity were included, but their conclusions were made separately.

Articles containing uncertain items were not excluded but subjected to a second screen. The second screen was performed by reading the abstract of articles that were not excluded at the first screen. The above-mentioned criteria were used for the abstracts. Articles with relevant abstract were subjected to a third screen. For the third screen, full length of all relevant articles were carefully read. All the above-mentioned criteria were considered again, together with extraction of the following characteristics: research aim, design of the study, the method of evaluation of surgical outcome, the number of receptivity markers investigated, investigation method of endometrium and uterine flushing samples, conclusion, and date of publication.

Outcome Measures

The primary outcome measure was change in endometrium receptivity markers after surgery. Therefore, only studies focusing on impact of BGDs surgery on endometrial

receptivity were considered for further evaluation. Publications evaluating endometrial receptivity in patients not going for surgery were out of scope of this study. Concordantly, studies evaluating endometrium and uterine flushing samples before and after surgery were chosen. Publications evaluating consequences of medical treatment on endometrial receptivity were considered as secondary outcome measures. The remaining studies were grouped according to their patients group (endometrioma, peritoneal endometriosis, leiomyoma, endometrial polyp, hydrosalpinges, uterine septum, adenomyosis, and endometrial injury), and then the effect of BGDs surgery on endometrial receptivity markers was evaluated and compared.

Results

Included Studies

The search of databases resulted in a total of 3051 titles. After the first and second screen based on title and abstract search, only evidently irrelevant publications (a total of 3009 items) were excluded because the publication failed to meet selection criteria. The third screen based on full text was performed in the remaining 42 publications. At this thorough investigation, 28 articles did not meet the selection criteria and were excluded. They were review articles or commentaries (n = 5) or retrospective trials (4) or case series (n = 3), lack of clear data (n = 7) or had outcomes not mentioned, or timing of intervention different or unclear (n = 9). The flowchart of selection is shown in Figure 1. Impact of BGDs surgery on endometrium receptivity was evaluated in 14 prospective clinical trials. All studies evaluated endometrial receptivity before and after surgery. We, therefore, performed data extraction only in 14 articles, where 5 of 14 articles were related to hydrosalpinges, 5 to endometriosis, 3 to endometrial polyp, and the remaining 1 to leiomyomas and uterine septum. The numbers of investigated receptivity markers were between 1 and 6. Of the 14 articles, 12 used endometrial samples for receptivity evaluation whereas 2 used uterine flushing samples. The RT-PCR, immunoradiometric assay, enzyme-linked immunoassays, and immunohistochemical staining methods were used to evaluate endometrium and uterine flushing samples. One study used cytotoxicity assays to investigate the effect of surgery on endometrium. Conclusion and date of publication are shown in Table 2.

Endometrial Receptivity After Endometriosis and Endometrioma Surgery

Both peritoneal endometriotic lesions and ovarian endometrioma may have a detrimental effect on the endometrial microenvironment.[3,4] Presence of endometriotic lesions may directly stimulate deregulation of receptivity markers which are responsible for implantation in the eutopic endometrium.[4,6] Surgical resection of minimal–mild endometriosis is an effective approach for the treatment of subfertility-associated superficial peritoneal endometriosis.[71,72] A randomized controlled trial

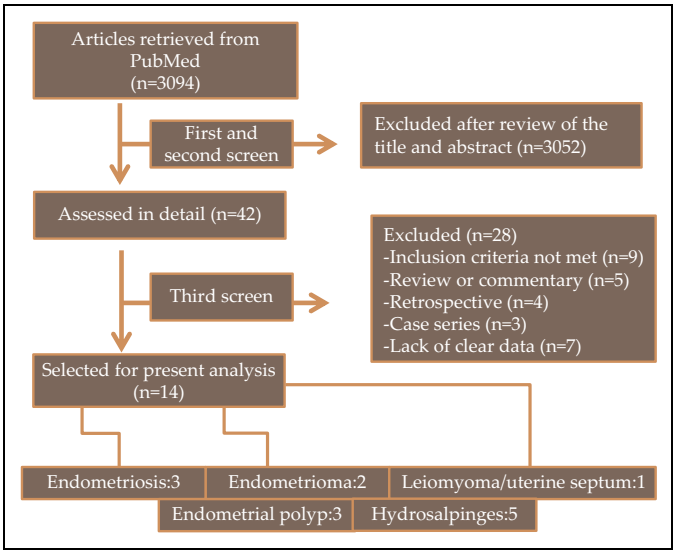

Figure 1. A flowchart depicting the selection of studies for the systematic review.

assessed fertility outcomes in stage I to II minimal or mild endometriosis and reported an improvement in live birth rate after surgical resection or ablation of visible implants.[71] Complete surgical excision of minimal–mild endometriosis before the ART treatment may improve reproductive outcome.[73] Likewise, complete removal of deeply infiltrating peritoneal endometriosis enhances fertility success.[74,75] However, whether surgical treatment of moderate-to-severe endometriosis can increase pregnancy rates are lacking. Barnhart et al demonstrated that women with severe endometriosis had significantly lower peak estradiol levels and number of oocytes retrieved as well as pregnancy rates than those with mild disease.[76] Even young women with severe disease have lower implantation rates when compared to those with minimal or mild diseases.[77] Nevertheless, recent retrospective study has reported that women with moderate–severe stage endometriosis have a good chance of pregnancy following laparoscopic resection.[78] In good agreement, a study conducted by Centini et al has demonstrated that laparoscopic excision of deep endometriosis increases pregnancy rate.[11]

It is a well-known fact that neither all women with endometriosis are infertile nor all women with endometriosis lack expression of endometrial receptivity markers.[79] Studies reported that superficial peritoneal endometriosis may lead to both defective methylation and decreased expression of endometrial HOXA-10 gene.[47,58] In contrast, endometrium αvβ3 integrin expression and pinopode formation in infertile patients with stage I or II endometriosis are not decreased.[80] Assessment of endometrial receptivity markers after surgical resection or ablation of superficial peritoneal endometriosis has been discussed in 3 investigations. In the first study, the correlation between minimal–mild endometriosis surgery and change in endometrium αvβ3 expression was discussed.[9] Treatment of women with superficial endometriosis by laser ablation of implants has been reported to have positive impacts

Table 2. Summary of Included Studies.

Studies	Surgical Intervention	Receptivity Markers	Comment
1. Celik et al (2015)[4]	• Endometrioma resection • Nonendometriotic cystectomy	HOXA-10, HOXA-11, LIF, ITGB3, ITGAV	• Endometrioma surgery increases expression levels of endometrial HOXA-10, 11 and LIF mRNA. • Unchanged receptivity markers expression
2. Celik et al (2013)[3]	• Endometrioma resection • Nonendometriotic cystectomy	NF-κB1 (p50/105), NF-κB p65 (Rel A)	• Endometrioma surgery decreases expression of NF-κB1 and NF-κB p65. • Unchanged NF-κB p65 expression
3. Lessey and Young (1997)[9]	Laser ablation of superficial endometrial implants	αvβ3	Returning of decreased endometrium integrin αvβ3 expression after surgery
4. Moberg et al (2015)[67]	Cauterization and excision of endometrial implants	LIF, LIFR, and gp130 protein	Any improvement in the failed expression of LIF, LIFR, and gp130 did not occur.
5. Oosterlynck et al (1994)[68]	CO_2-laser excision of the endometriotic implants	Cytotoxicity assays in autologous and heterologous endometrial lymphocytes	Decreased natural killer cell activity and impaired cytotoxicity did not change.
6. Unlu et al (2016)[7]	Intramural myomectomy	HOXA-10 HOXA-11, LIF, ITGB3, and ITGAV genes	Intramural myomectomy upregulates expression levels of endometrial HOXA-10 and HOXA-11 mRNA.
	Submucosal myomectomy		Submucosal myomectomy leads insignificant upregulation in endometrial HOXA-10 and HOXA-11 mRNA expression.
	Metroplasty		Metroplasty does not alter expression levels of endometrial receptivity markers.
7. Meyer et al (1997)[8]	• Surgical extirpation • Distal neosalpingostomy • Transvaginal needle drainage • Proximal tubal ligation of the hydrosalpinges.	• Integrin α1β1 • Integrin α4β1 • Integrin αvβ3 • Gland/stroma • synchronization	(i) Surgery improved the failed expression of integrin αvβ3 in the endometrium of 70% patients. (ii) Surgery leads to reduction in the gland stroma dyssynchrony and out-of-phase endometrium.
8. Bildirici et al (2001)[69]	Salpingectomy	αvβ3	Improvement in the expression of endometrial integrin αvβ3 following salpingectomy.
9. Seli et al (2005)[17]	Salpingectomy	LIF	LIF levels of the postsalpingectomy samples reached to the levels of age-matched fertile controls.
10. Daftary et al (2007)[16]	Salpingectomy	HOXA-10	Salpingectomy leads to 15-fold increase in endometrial HOXA-10 expression.
11. Zhong et al (2012)[70]	• Salpingectomy • Hydrosalpinx aspiration • Salpingostomy • Proximal tubal ligation	LIF, L-selectin	Hydrosalpinges surgery increased the expression of endometrial LIF and L-selectin ligand.
12. Elbehery et al (2011)[10]	Polypectomy	IGFBP-1, glycodelin	Polypectomy upregulates the IGFBP-1 and glycodelin levels in endometrial flushing samples
13. Ben-Nagi et al (2009)[42]	Polypectomy	IGFBP-1, TNF-α, osteopontin, glycodelin, IL-6, and IL-10	(i) Polypectomy improved failed expression of IGFBP-1, TNF-α, and osteopontin in flushing samples. (ii) Unaltered glycodelin, IL-6, and IL-10 levels after polypectomy
14. Bozkurt et al (2015)[43]	Polypectomy	NF-κB1 and NF-κB p65	Polypectomy leads to significant decline in both endometrial NF-κB1 and NF-κB p65 expressions

Abbreviations: NF-κB, nuclear factor κB; HOX, homeobox; LIF, leukemia inhibitory factor; IL, interleukin; TNF-α, tumor necrosis factor α; IGFBP-1, insulin-like growth factor 1 binding protein; LIF-R, leukemia inhibitory factor receptor; mRNA, messenger RNA; ITGAV, integrin subunit alpha V; ITGB3, integrin subunit beta 3.

on the return of decreased endometrium integrin αvβ3 expression and improved fertility.[9] Nevertheless, the study could be criticized because the GnRH analog treatment was used after endometriosis surgery. Suppression of chronic inflammation with GnRH analog has been noted to improve in vitro fertilization (IVF) outcomes.[81]Concordantly, Lessey reported that administration of a GnRHa to women with stage I/II endometriosis having disturbed endometrial β3 integrin expression resulted in normalization of expressions in about two-third of the patients.[81] Treatment of patients having superficial endometriosis with GnRHa improves the IVF outcome and further supports beneficial role of analogs.[82] Moreover, Ruan et al demonstrated that, in a murine model, failed endometrial β3 integrin and LIF expression were partially improved after GnRHa treatment.[83] Together, returning of failed integrin expression after combined treatment with surgery and analogs restrict to make a further comment regarding the impact of surgery for superficial endometriosis on endometrial integrin expression.

In the second study, Moberg et al measured the LIF, LIF receptor (LIFR), and glycoprotein 130 (gp130) immunostaining in the eutopic endometrial samples that were taken from 65 subfertile women with the revised American Society for Reproductive Medicine stage I to II disease before and after laparoscopy.[67] In all, 23 healthy women undergoing laparoscopic tubal ligation were accepted as controls. During laparoscopy, peritoneal endometriotic implants were cauterized or excised, and adhesiolysis was performed. They reported reduced endometrial LIF, LIFR, and gp130 protein expression before endometriosis surgery. Following surgery, they did not find any improvement in the failed expression of LIF, LIFR, and gp130. The LIF is the first endometrial receptivity marker to be conclusively accepted as critical for blastocyst implantation.[84] Expression levels of endometrial LIF and its gp130 receptor are upregulated in response to human chorionic gonadotrophin treatment.[85]Nevertheless, Moberg et al study could be criticized because only 24 (36.4%) of the 65 participants agreed to have a second endometrial biopsy. More important handicap of this study was the timing of second endometrial biopsy which were obtained after postoperative goserelin treatment.

In the third study, to detect whether natural killer activity of eutopic endometrium changes after the CO_2-laser excision of the endometriotic lesions, Oosterlynck et al performed cytotoxicity assays in 15 women having endometriosis.[15] Endometrial samples were obtained before and 3 to 4 months after CO_2-laser excision of the superficial endometriotic lesions. Authors reported that after complete removal of the endometriotic implants, decreased natural killer cell activity and impaired cytotoxicity in both autologous and heterologous endometrial lymphocytes remained unaltered.[68]

Assessment of endometrial receptivity markers after endometrioma resection has been discussed in 2 studies conducted by our group. We demonstrated that surgical removal of uni- or bilateral ovarian endometriomas improved the pathological expression of some endometrial receptivity markers.[3,4]In the first clinical study, we investigated the possible relationship between ovarian cystectomy and eutopic endometrial inflammation in 15 infertile women with endometrioma and 10 women with nonendometriotic cyst undergoing laparoscopic surgery.[3] In all, 10 healthy women without ovarian cyst were included as controls. We measured the expression levels of NF-kB1 (p50/p105) and NF-kB p65 (Rel A) in the eutopic endometrium before and 3 months after laparoscopic removal of the endometrioma during the mid-secretory phase. Expression levels of endometrial NF-kB1 (p50/105) in women with endometrioma were found to be significantly higher compared to both nonendometriotic benign ovarian cysts and fertile controls. Laparoscopic endometrioma cystectomy resulted in a significant decline in expression levels of NF-kB1. Likewise, immunoreactivity of NF-kB p65 (Rel A) in the eutopic endometrium decreased significantly subsequent to the surgical removal of the endometrioma.

Physiological amount of endometrial inflammation is necessary for successful embryo implantation. Progesterone stimulus is essential for the decidualization and the establishment of endometrial receptivity.[86] Progesterone influences the expression of HOXA-10 and HOXA-11 in the mid- and late secretory endometrium.[2,87] In contrast, by leading progesterone resistance, pathological endometrial inflammation may impair receptivity of eutopic endometrium.[3,88] Therefore, the loss of physiologic pattern of NF-kB expression could be responsible for the progesterone resistance in the endometrioma. Thus, laparoscopic removal of endometrioma, similar to salpingectomy in hydrosalpinx, may improve the endometrium by decreasing the NF-kB levels during the implantation window. The interval necessary for the resolution of the inflammation after the treatment depends on the degree of inflammatory reaction. Nevertheless, the 3-month interval resulted in a significant decrease in the endometrial NF-kB levels after the endometrioma removal.

As HOXA10 directly affects expression pattern of some receptivity genes including αvβ3 integrin, pinopods, and estrogen receptors, in the second study, we investigated whether surgical removal of endometrioma alters HOX genes, integrins, and LIF messenger RNA (mRNA) expression in the endometrium of 20 infertile women with endometrioma, 5 women with nonendometriotic benign ovarian cyst, and 5 fertile controls without cyst.[89] We evaluated expression levels of endometrial HOXA-10, HOXA-11, LIF, ITGAV, and ITGB3 genes before and after laparoscopic removal of the endometrioma during the mid-secretory phase.[4] Endometrial sampling was performed at the time of surgery. Second endometrial biopsies were obtained 3 months after laparoscopic endometrioma resection. Expression levels of all genes were lower before the surgery. However, their differences failed to show statistical significance excluding ITGAV.

Surgical removal of endometriomas upregulated the expression levels of endometrial HOXA-10, HOXA-11, and ITGAV mRNA. Compared to preoperative fold-change values, significantly increased HOXA-10 and HOXA-11 mRNA expression were noted after surgery. We detected 12.1-fold increase in endometrial HOXA-10 mRNA and 17.2-fold increase in

endometrial HOXA-11 mRNA expression. This postoperative increment in endometrial HOXA-10, and HOXA-11 mRNA was statistically significant ($P < .008$ and $P < .035$, respectively). Fold change in endometrial ITGAV mRNA after endometrioma surgery was found to be 30.1. However, this fold increase was insignificant. Both endometrial LIF and ITGB3 mRNA expression have not changed significantly after endometrioma surgery.

However, we do not know whether this increase in endometrial HOXA-10 and HOXA-11 mRNA expressions after endometrioma surgery is associated with removal of endometrioma or a consequence of other factors associated with the disease. Upregulation of HOXA-10 and HOXA-11 mRNA cannot be a direct result of endometrioma resection but rather an outcome of surgery-induced stress. To exclude this, in our study, all endometrial samples were obtained 3 months after endometrioma surgery. Moreover, HOXA-10 and HOXA-11 mRNA expression have not changed significantly after nonendometriotic cyst resection, suggesting surgical stress alone does not affect the expression of endometrial HOX genes. Several mechanisms may be responsible for increased HOX gene expression after endometrioma surgery. Disturbed progesterone receptor expression in endometriosis may lead to diminished progesterone response and decreased expression of progesterone-responsive HOXA-10 and HOXA-11 genes.[2,58] In this sense, endometrioma surgery might improve progesterone resistance and may lead to increased endometrial HOXA-10 and HOXA-11 mRNA expression. Another mechanism proposed is the epigenetic changes and hypermethylation of the HOXA-10 and HOXA-11 genes.[58] Hypermethylation of the 5′ promoter region of HOXA-10 gene and decreased expression were demonstrated in the eutopic endometrium.[47,58] In addition, chronic inflammation which is main component of endometriosis, can lead to epigenetic changes.[90] A common concept that is emerging related to eutopic endometrial receptivity is based on the pathological endometrial inflammatory changes that occur in response to endometriosis or endometrioma.[3,91] Taken together, we can suggest that interruption of pathological inflammation in endometrium by laparoscopic removal of endometrioma may inhibit hypermethylation of HOXA-10 and HOXA-11 genes and increases their expression.

As opposed to our results, studies associated with oocyte donation demonstrated that endometriosis is not detrimental to embryo implantation in oocyte recipients.[13,92] For this reason, one may believe that presence of endometrioma does not significantly impair the endometrial microenvironment then someone can also say that there is no need for endometrioma surgery. Nevertheless, conception of a patient after oocyte donation does not mean that endometrium is certainly healthy. It should be remembered that good quality oocytes come from any healthy donors may come through endometriosis-associated implantation defect. Moreover, pretreatment of recipients having endometriosis with GnRH analogues might improve the endometrial impairment. Study of Lessey and Young supports our hypothesis.[9] They have demonstrated that treatment of women having endometriosis with GnRH analogues improves fertility.[9]

Endometrial Receptivity After Myomectomy

Depending on their localization, submucosal leiomyomas (SMs) and intramural leiomyomas (IMs) have been implicated in the infertility etiology.[93,94] It is well known that host myometrium of the myomatous uterus differs from normal myometrium.[95] In agreement, several hypotheses including inhibition of sperm and blastocyst transport, dysfunctional uterine contractility, increased estrogen receptor concentration within the myometrium, and defective implantation have been suggested to explain how leiomyomas cause infertility, but none is definitive.[96-98] All of these may lead to disturbed subendometrial contractions. Nevertheless, a comprehensive review by Donnez and Jadoul highlighted the lack of scientific evidence necessary to establish a causal relationship between leiomyomas and infertility or to evaluate the potentially beneficial effects of myomectomy on reproductive outcome.[99] In contrast, significantly lower implantation and pregnancy rates have been reported in women with submucosal leiomyomas.[100] Concordantly, myomectomy of submucosal leiomyoma increases pregnancy rate of these patients.[101,102] Likewise, reduced implantation and pregnancy rates have been noted in women with intramural fibroids, even in the normal endometrial cavity, and surgical removal of intramural fibroids improves endometrial receptivity.[3,100,103] Unlikely, subserosal leiomyomas do not affect pregnancy rates.[103]

To date, it remains to be clarified whether surgical treatment of uterine fibroids improves endometrial receptivity. Most of the researchers have shown a better reproductive outcome after myomectomy, and the difference is evident when the leiomyoma was the only identifiable cause of infertility.[104,105] However, increased pregnancy rates following myomectomy are based on only clinical observations. We, therefore, have little information on how myomectomy improves fertility, and little is known which molecular events occur inside the endometrium following myomectomy.

Assessment of endometrial receptivity markers following leiomyoma removal has been performed in only 1 study which was conducted by our group. We designed a clinical study to investigate whether endometrial receptivity genes are altered in infertile patients with intramural leiomyomas not distorting the endometrial cavity undergoing myomectomy. We have measured the expression levels of endometrial HOXA-10, HOXA-11, LIF, ITGB3, and ITGAV mRNA before and after myomectomy during mid-luteal phase in participants with intramural leiomyomas ($n = 7$), submucosal leiomyomas ($n: = 7$), and fertile participants without fibroids ($n = :7$). First endometrial sampling was obtained at the time of surgery and second sampling was obtained 3 months after myomectomy. A trend toward decreased endometrial HOXA-10, HOXA-11, and ITGAV mRNA expression was detected in both SM and IM groups before myomectomy when compared to the fertile group. However, the differences failed to show statistical

significance. Likewise, there were no statistically significant differences between the SM and the IM groups in terms of endometrial HOXA-10 and HOXA-11 mRNA expression levels before surgery. Following myomectomy of IM, we have detected 12.8-fold increase in endometrial HOXA-10 mRNA expression and 9.0-fold increase in endometrial HOXA-11 mRNA expression. This increase in both endometrial HOXA-10 and HOXA-11 mRNA expression were found to be significant. After myomectomy of IM, we have detected 26.0-fold increase in endometrial LIF mRNA, 15.9-fold increase in endometrial ITGB3 mRNA, and 2.81-fold increase in endometrial ITGAV mRNA expressions. However, these fold-change values of LIF, ITGB3, and ITGAV mRNA were insignificant.

Surgical removal of SM leads to insignificant upregulation in endometrial HOXA-10 and 11 mRNA expressions. Insignificant downregulation was also detected in the LIF and ITGAV mRNA expression after submucosal myomectomy. We have also noted insignificant upregulation in ITGB3 mRNA expression after submucosal myomectomy.

Significant upregulation of endometrial receptivity markers after intramural myomectomy lead us to believe that intramural leiomyomas which do not distort the endometrial cavity may disturb the endometrial receptivity. Reduced implantation and pregnancy rates in women with intramural leiomyomas may be secondary to impaired endometrial BMP-2 expression. Sinclair et al have reported that leiomyoma-derived TGF-β3 induces BMP-2 resistance in endometrium and leads to disturbance on endometrial decidualization.[37] They also showed that treatment of leiomyoma-associated endometrial stromal cells with recombinant human BMP-2 caused the decline in both HOXA-10 and LIF genes expression. Interestingly, inhibition of TGF-β signaling using TGF-β antibody restored BMP-2 stimulated expression of HOXA10 and LIF genes.[38] These results support the presence of BMP-2 resistance in leiomyoma-associated endometrial stromal cells.[38,106] Abovementioned studies and our results when taken together show interruption of TGF-β signaling may be a potential approach to improve reduced implantation rates associated with leiomyomas. Accordingly, leiomyoma-derived TGF-β signals can be prevented by either medical treatment or surgical intervention. For now, we do not have any drug that will stop these signals. The only alternative we have is to remove leiomyomas by surgery. Because TGF-β3 is secreted in large amounts by uterine fibroids, surgical removal of intramural leiomyomas inhibits secretion of TGF-β3 and prevents BMP-2 resistance and increases the expression of HOXA-10 and HOXA-11 mRNA.[39] As a consequence, we can strongly suggest that myomectomy of intramural leiomyomas may increase endometrial receptivity by restoring endometrial BMP-2 resistance. Together, we may conclude that there is a direct link between the intramural leiomyomas and the infertility, and we can vigorously hope to improve fertility by surgically removing of the intramural leiomyomas.

Insignificant upregulation of endometrial receptivity genes after submucosal myomectomy can be attributed to the intramural remnants of the submucosal leiomyomas. In our clinical practice, intramural portion of some submucosal leiomyoma could not be fully removed during hysteroscopic myomectomy. Data supporting our ''intramural remnants'' hypothesis comes from 2 different studies. Horcajadas et al have showed that endometrial GPx3 gene expresses abnormally in the presence of small intramural leiomyomas, suggesting that endometrial receptivity may be disturbed in the presence of the small intramural lesions.[106] Consistent with this, Khalaf et al have reported that the presence of small leiomyomas are associated with reduced ongoing pregnancy rates in IVF-ET.[107] Hence, the remaining parts of the submucosal leiomyomas after myomectomy might continue to send the diffusible signaling molecules that cause the persistence of endometrial receptivity defect. However, before concluding, submucosal myomectomy does not improve the endometrial molecular defects involved in implantation, a comparison of receptivity markers should be made between patients with submucosal fibroids which were surgically removed as complete and incomplete. Different origin of submucosal fibroids may also explain the unimproved endometrial receptivity after submucosal myomectomy. Concordantly, submucous leiomyomas arise from junctional zone myocytes and are distinct from intramural and subserosal leiomyomas.[107]

Endometrial Receptivity After Uterine Septum Resection

Uterine septum is the most common type of congenital uterine malformation, approximately with 80% to 90% of all uterine malformations. It has been reported that presence of septate uterus may cause infertility.[108,109] Studies reported that defective blood supply to the uterine septum makes septum unsuitable for a successful implantation and might lead to spontaneous miscarriage.[110,111] Hysteroscopic septum resection is a simple and safe approach for the removal of the uterine septum.[108,109] Metroplasty improves fertility outcomes after a diagnosis of uterine septum in women having a history of miscarriages and infertility.[109,110,112,113] In a recent study, Tomazevic et al.have reported that the pregnancy rates before metroplasty are lower than after metroplasty in women undergoing in vitro fertilization.[114]

Although studies have confirmed the validity of metroplasty to improve reproductive functions they did not evaluate the preoperative and postoperative endometrial receptivity change and concluded improved pregnancy rate after surgery based on only clinical observations.[109,110,115,116] Unfortunately, there is no comprehensive endometrial study investigating the effects of metroplasty on expression patterns of endometrial receptivity markers. The possible impacts of uterine septum resection on endometrium receptivity were analyzed only in 1 publication from our group. In this study, we have measured expression levels of endometrial HOXA-10 HOXA-11, LIF, ITGB3, and ITGAV mRNA before and after metroplasty during mid-luteal phase in 7 participants with septate uterus.[7] The diagnosis of septate uterus was made by American Society for Reproductive Medicine classification criteria.[117] We have shown that endometrial receptivity markers upregulated in women with uterine septum before the surgery. However, this

upregulation does not reach statistical significance. Likewise, expression levels of receptivity markers were found to be unchanged after septum resection, suggesting preserved endometrial receptivity in patients having uterine septum. Our study could be criticized because of the small sample size and lack of power to address our hypothesis, but overall we did not see any significant change in receptivity status of endometrium after metroplasty. In light of this information, one might think that the reason for the increase in pregnancy rates after uterine septum resection may be due to mechanical factors rather than endometrial receptivity defect.[7]

Endometrial Receptivity After Hydrosalpinges Surgery

Despite progress in ART, studies have reported that women with hydrosalpinges have difficulty in conceiving.[118,119] It has been reported that leakage of hydrosalpinx fluid into the endometrial cavity exerts detrimental effect on both embryo growth and sperm survival.[40,41] Treatment of uni- or bilateral hydrosalpinges by surgical interventions such as extirpation, drainage, or proximal tubal ligation could increase implantation rates and lead to decline in early embryo loss.[52,118,119]

The impact of hydrosalpinges surgery on endometrium receptivity were individually analyzed in 5 publications. In a first study conducted by Meyer et al,[8] patients with unilateral or bilateral hydrosalpinges underwent an endometrial biopsy before and after hydrosalpinges surgery. Endometrial samples of 103 cases having hydrosalpinges were compared to 55 infertile and 44 fertile controls. Fluid-filled hydrosalpinges lead to the failed expression of integrin αvβ3 in the endometrium of 63 patients before surgery.[8] However, expressions of endometrium α1β1 and α4β1 were found to be normal before surgery. Different surgical approaches such as extirpation, distal neosalpingostomy, transvaginal needle drainage, and proximal tubal ligation of the hydrosalpinges were performed. In all, 20 of 63 participants with hydrosalpinges having impaired expression of the αvβ3 underwent second endometrial biopsy 3 months after the surgery. In all, 15 of 20 endometrial samples demonstrated an increase in overall αvβ3 expression after surgery. Neosalpingostomy, ligation, and aspiration of fluid were less successful in restoring endometrial receptivity than in the salpingectomy. Authors also noted that salpingectomy led to a reduction in both gland/stromal dyssynchrony and out-of-phase endometrium.[8]

Similar results were noted in 10 women undergoing surgery for communicating hydrosalpinges by Bildirici et al.[69] They reported an improvement in the expression levels of endometrial integrin αvβ3 following salpingectomy.Likewise, Seli et al examined the expression levels of LIF in the endometrium of infertile women with both uni- or bilateral hydrosalpinges prior to and following salpingectomy.[17] Endometrial expression levels of LIF in women having hydrosalpinx increased after salpingectomy. Surgery for hydrosalpinx led to increase in total H-score for LIF expression in 8 of 10 cases with hydrosalpinx.[17] Moreover, LIF levels of the postsalpingectomy samples reached the levels of age-matched fertile controls (n = 10).A study conducted by Daftary et al evaluated HOXA-10 expression levels in the endometrium of 9 infertile women with unilateral or bilateral hydrosalpinx and in 6 fertile controls.[16] Expression levels of HOXA-10 gene were measured during the midsecratory phase in endometrium of patients with hydrosalpinges before and after salpingectomy. They demonstrated that expression levels of endometrial HOXA-10 was downregulated in patients with hydrosalpinx before surgery. Salpingectomy culminated in 15-fold increase in endometrial HOXA-10 expression. Immunohistochemical analysis of endometrial samplings is in agreement with the real-time reverse transcription polymerase chain reaction findings. They also noted that endometrial HOXA-10 expression was upregulated to normal levels 4 months after salpingectomy. Fifth study by Zhong et al investigated the impact of different hydrosalpinges surgeries on the expression levels of endometrium of LIF and L-selectin ligand. In all, 60 patients with hydrosalpinx and 30 patients with tubal obstruction were collected. Immunohistochemical analysis of endometrium was performed before and after hydrosalpinges surgery.[70] They found markedly reduced LIF and L-selectin ligand expression in the endometrium of patients with hydrosalpinges before surgery. After surgery, LIF and L-selectin ligand of women having hydrosalpinx was comparable to that of patients with tubal obstruction. Isolatedly, surgical treatment of women having fallopian tube with phimosis has been reported to improve fertility rates.[51]

Taken together, we suggest that HOXA10, LIF, L-selectin, and αvβ3 integrin expression in response to hydrosalpinx fluid as a potential molecular mechanism for diminished implantation rates in women with uni- or bilateral hydrosalpinx. Primarily salpingectomy after other surgical interventions restore endometrial HOXA10, LIF, L-selectin, and αvβ3 integrin expressions. This may be 1 mechanism by which salpingectomy results in augmented implantation rates in IVF. Improvement in reproductive outcomes of women with inflammatory hydrosalpinges following different surgical approaches may be due in part to an increase in endometrial expression of these receptivity markers.

Endometrial Receptivity After Endometrial Polypectomy

Endometrial polyp (EP) is the localized hyperplastic overgrowths of endometrial glands and stroma.[120] Up to 25% of women with otherwise unexplained infertility exhibit endometrial polypduring hysteroscopic evaluation.[120-122] Endometrial polyps not only lead to mechanical interference with sperm and embryo but also may alter endometrial receptivity and implantation. Relevantly, endometrial Polypshave decreased expression of progesterone receptors that might culminate in progesterone resistance. This can lead to abnormalities in the secretion of progesterone-regulated receptivity markers.[123]

However, their effect on endometrial receptivity and the impact of polypectomy on fertility outcome is unclear. Many authors believe that hysteroscopic polypectomy may improve fertility in these women. Recent prospective randomized study reported a significant improvement in pregnancy rates after

hysteroscopic polypectomy.[124]Likewise, 3 nonrandomized studies also noted an association between polypectomy and increased spontaneous pregnancy rates.[125-127] Studies investigating the polyp size or number demonstrated that hysteroscopic polypectomy improved reproductive outcome in previously infertile women, regardless of the number or size of endometrial polyps.[122,128] In contrast, polyps smaller than 2 cm in size did not cause any impairment of pregnancy rates in women undergoing IVF.[129,130] Nevertheless, Lass et al noted increased miscarriage rate in women with endometrial polyp smaller than 2 mm and recommended embryo cryopreservation.[130]

Great majority of endometrial polypectomy studies did not evaluate endometrium receptivity after surgery. The impact of hysteroscopic polypectomy on endometrium receptivity was individually analyzed in 3 publications. Elbehery et al measured the levels of IGFBP-1 and glycodelin in endometrial flushings obtained from 100 infertile women with endometrial polyp and 150 women having a history of menorrhagia resistance to medical approaches[10] Endometrial flushing samples were collected before and after hysteroscopic polypectomy. The expression levels of endometrial IGFBP-1 and glycodelin were found to be significantly lower before polypectomy. Hysteroscopic polypectomy reversed the IGFBP-1 and glycodelin levels in postpolypectomy endometrial samples.[10] Ben-Nagi et al[42] performed similar study in uterine flushing samples obtained from 20 women with endometrial polyps and had a similar conclusion. They found decreased mid-secretory IGFBP-1, TNF-α, and osteopontin levels in uterine flushing samples. Following hysteroscopic polypectomy, defective expression of IGFBP-1, TNFα, and osteopontin levels improved.[42] Nevertheless, they did not find any differences in the concentrations of glycodelin, IL-6, and IL-10 in paired samples prior to and postpolypectomy. In a recent study, Bozkurt et al evaluated the expression levels of endometrial NF-κB1 and NF-κB p65 in 15 women with endometrial polyp, 5 women with unexplained infertility, and 5 fertile controls. Expression of NF-κB1 and NF-κB p65 was measured before and after hysteroscopic polypectomy during the mid-secretory phase.[43] They reported that NF-κB1 and NF-κB p65 expression levels in prepolypectomy samples were significantly higher compared to both unexplained infertile and fertile controls. Hysteroscopic polypectomy leads to significant decline in endometrial NF-κB1 and NF-κB p65 expression.[43] Together, EPs not only lead to defective expression of some receptivity markers but also give rise to pathological endometrial inflammation. Hysteroscopic polypectomy restores the defective endometrium in regard to receptivity markers and normalizes endometrial inflammation. Additionally, endometrial injury occurring secondary to polypectomy may also participate in the development of a receptive endometrium.

Endometrial Receptivity After Adenomyosis Surgery

So far, the impact of adenomyosis surgery on endometrium receptivity remains elusive. Conflicting results were obtained regarding endometrium receptivity in cases with adenomyosis. Some studies demonstrated that both HOXA10 and LIF gene expression are significantly decreased in women with adenomyosis.[131,132] In contrast, overexpression of IL-6 and cytochrome P450 have been reported in patients with adenomyosis suggesting dysfunctional endometrium.[133,134] Moreover, both dysregulated estrogen receptor β expression and the lack of PR expression might contribute to the defective endometrium seen in patients with adenomyosis.[59] Unfortunately, there is no study investigating possible impact of adenomyosis surgery on endometrium receptivity in human or animal model of adenomyosis. Hence, little is known on alterations in receptivity markers in women with adenomyosis undergoing surgery, and knowledge is based on clinical observations seen in cases with endometriosis.[135]

Endometrial Receptivity After Endometrial Injury

Studies demonstrated that local injury to endometrium such as biopsy, scratches, and hysterscopy increase implantation and pregnancy rates in subsequent IVF cycles.[136-138] There are several possible mechanisms by which endometrial manipulation may increase endometrium receptivity. Local injury of endometrium may trigger decidualization, wound healing, cytokines and growth factors secretion, and accumulation of stem cells within the injured endometrial areas.[139,140] Mechanical manipulation of endometrial cavity which is associated with improved decidualization is not a new phenomenon. For example, scratching the endometrium, oil injection into the endometrial cavity, suturing the uterine horn of some animals, and scar tissue secondary to cesarean section induced a rapid growth of decidualization.[141-144] Concordantly, by inducing inflammatory events, endometrial injury regulates the local expression of receptivity genes and cytokines, suggesting improved decidualization and embryo implantation.[145] Likewise, accumulation of macrophages, dendritic cells, and immune cells within the injured endometrium further supports the implantation rates.[146] Recent meta-analysis reported that in cases with implantation failure, there is enhanced pregnancy outcome with local endometrial injury performed in the cycle preceding controlled ovarian stimulation.[147] Nevertheless, before recommending the routine use of local endometrial injury in the women with implantation failure, we have to find answers for some questions such as timing of local injury, use of hysteroscopy or endometrial scratching, and preference of single or multiple endometrial injury.[147]

Endometrial Receptivity After Nonendometriotic Benign Ovarian Cystectomy

The effects of nonendometriotic benign ovarian cysts on endometrium receptivity were individually analyzed as a control group in 2 publications from our group.[3,4] We did not find any alteration in the expression levels of endometrial HOXA-10, HOXA-11, ITGB3, ITGAV, and LIF mRNA after surgical removal of nonendometriotic benign ovarian tumors including,

serous, dermoid, and mucinous cysts.[4] Likewise, there was no statistically significant difference in the endometrial NF-kB p65 (Rel A) expression after the benign ovarian cystectomy.[3]

Impact of BGDs Surgery on Ovarian Reserve

Several studies revealed that cystectomy for ovarian endometriomas lead to a decrease in ovarian reserve, especially in cases of bilateral endometriomas. Disturbance of the blood supply after surgery has been considered one of the reasons to affect ovarian reserve in endometrioma cystectomy. Uni- or bilateral laparoscopic endometrioma cystectomy lead to a significant decline in serum levels of AMH than cystectomy for other benign nonendometriotic ovarian tumors.[148,149] Likewise, laparoscopic cystectomy for bilateral endometriomas have been reported to cause a greater decline in serum AMH levels than unilateral cystectomy.[148,149]

Similar to endometrioma resection, laparoscopic cystectomy for nonendometriotic benign ovarian tumors lead to a significant decline in AMH levels after surgery.[149] Nevertheless, decline in serum AMH levels after benign ovarian cystectomy has been reported to be lower than those observed after endometrioma cystectomy.[148] Conversely, the rate of AMH decline at 3 months after laparoscopic cystectomy has not been found to differ between the endometrioma and the other benign ovarian cysts.[150]

Similar to endometrioma surgery, hydrosalpinx surgery may result in decreased blood supply to both ovaries. Nevertheless, the ovarian response after prophylactic salpingectomy was not impaired.[151] Ni et al reported that serum AMH levels of patients who underwent bilateral salpingectomy, unilateral salpingectomy, bilateral interruption in the proximal oviducts, and bilateral oviduct obstruction were similar.[152] Consistent with above-mentioned study, Findley et al reported that mean AMH levels were not significantly different at 4 to 6 weeks postoperatively or 3 months postoperatively among women with salpingectomy versus no salpingectomy.[153] In contrast, Grynnerup et al showed that AMH levels were significantly lower in the salpingectomy group than in the nonsalpingectomy group.[154]

Discussion

For better understanding of the underlying molecular mechanisms of BGDs-associated subfertility, we must turn our attention to the endometrium.[4] So far, it remains unexplained why some women with BGDs are infertile, whereas others are not. Understanding the interactions between BGDS and endometrium may shed light on this subject. We can suggest that not all women with endometriosis, endometrioma, leiomyomas, and hydrosalpinges exhibit abnormal endometrium. Some women with BGDs might have endometrial receptivity defects that alter embryo implantation, whereas others have normal endometrium. If endometrial receptivity defects are a consequence of the disease located in the peritoneum, myometrium, or ovary as demonstrated by human and baboon studies, surgical excision of BGDs might have beneficial impact on eutopic endometrium.[3,4,6,11,47]

Both hydrosalpinges and endometriosis have been associated with decreased IVF success, and surgical correction of both is associated with an improvement in subsequent pregnancy outcomes.[76,151,155,156] A reduction in normal expression levels of secretory phase endometrial HOXA, LIF, $\alpha v\beta 3$ integrin, and L-selectin, and an increase in inflammatory molecules including NF-kB predict poor reproductive outcomes and may reflect an inflammatory basis for BGDs. Concordantly, inflammatory cytokines present in the peritoneal fluid of patients with endometriosis/endometrioma and tubal fluid of patients with hydrosalpinges may alter normal endometrial function and account for the aberrant expression of some receptivity molecules in otherwise "in phase" endometrium. Some intermediate molecules produced by leiomyomas, endometriomas, or superficial endometriosis may reach to the endometrium via local diffusion or systemic circulation and disturb the endometrial receptivity. Increased levels of both peritoneal fluid and serum CA-125 in women with endometriosis and increased secretion of TGF-$\beta 3$ from leiomyomas might support this hypothesis. In good agreement, it has been reported that TGF-$\beta 3$ induces BMP-2 resistance in endometrium and leads to abnormal decidualization and receptivity defect.[37] Myomectomy may inhibit leiomyoma-derived TGF-β secretion and resume BMP-2 stimulated expression of HOXA-10 and LIF.[38]

Incomplete removal of any benign lesion located near or remote from endometrium may explain why some women have failed to observe improvement in pregnancy rates after surgical treatment of BGDs. Accordingly, the remaining parts of the BGDs after surgery may continue to secrete and send the harmful cytokines and diffusible signaling molecules which cause the persistence of endometrial receptivity defect. Clinical and laboratory findings support our idea. Accordingly, treatment failure seen in cases with hydrosalpinges were mostly related to reaccumulation of the hydrosalpinx fluid which occurs secondary to incomplete surgery. Similarly, persistence of high serum CA-125 levels following incomplete surgical excision or ablation of superficial or ovarian endometriosis further supports our opinion.

Although it is not mentioned in most polypectomy studies, we see the benefits (possible causes) of endometrial alteration following polypectomy. Polypectomy studies obviously demonstrated that hysteroscopic resection of endometrial polyps improved the expression of implantation markers. However, it is not clear whether the hysteroscope itself produces endometrial injury or whether the distending medium would have an impact on expression of receptivity markers. This needs to be clarified with comprehensive studies.

Collection of all studies which evaluate the impacts of surgical intervention for different infertile women having BGDs on endometrium receptivity strengthens this review. Weaknesses include the nonuniform surgical treatment protocols of women after the first endometrial biopsy was performed. The types of surgical intervention and measured receptivity markers did differ between the groups; therefore, we believe that

this did alter the outcomes or the conclusions of the study. Although contains some limitations, this review involved the systematic collection of articles to assess endometrium receptivity in relation to surgical treatment of BGDs. As we reviewed manuscripts for this article, the following results were demonstrated: (1) the influence of ablation or resection of superficial endometriosis on endometrium receptivity remains controversial; (2) cystectomy for endometriomas increased the expression levels of endometrial αvβ3 integrin, HOXA-10, and HOXA-11 mRNA; (3) myomectomy for intramural leiomyomas not distorting endometrial cavity tends to increase the expression levels of endometrium HOXA-10 mRNA more significantly than that for myomectomy for submucosal leiomyomas, (4) different form of hydrosalpinx surgery increased the expression levels of endometrial αvβ3 integrin, LIF, L-selectin, and HOXA-10; (5) by leading decreased pathological endometrial inflammation and increased receptivity markers hysteroscopic polypectomy could be the responsible factor that improved endometrium receptivity; and (6) there are insufficient evidence to draw a conclusion about the impact of adenomyosis removal, uterine septum resection, and benign ovarian cystectomy of nonendometriotic cysts on endometrium receptivity.

Conclusion

Although positive impacts of surgery on fertility outcome have been described, individual function and role of BGDs surgery on the network of endometrial receptivity are still not fully understood. Disturbed expression of some well-known endometrial receptivity markers in patients with BGDs are suggestive of impaired endometrial receptivity in these women. Surgical treatment of BGDs not only overcomes anatomical distortion caused by the disease but also has a perceptible impact on the alteration in receptivity gene expressions, cytokine concentrations, or other local inflammatory molecules that may inhibit conception. These findings provide molecular data to support some clinical findings that pregnancy rates improve after surgical resection of BGDs. Finally, prophylactic salpingectomy, intramural myomectomy, local endometrial injury, and hysteroscopic polypectomy improve endometrium receptivity. Unfortunately, there are currently insufficient data evaluating the impact of surgical resection of adenomyosis, uterine septum, and nonendometriotic benign ovarian cysts on endometrium receptivity.

Because of the difference in the methods used for analyzing endometrium, the receptivity markers, and the timing in relation to endometrial sampling, there was considerable heterogeneity in the included studies. The reliability of these conclusions, therefore, can be questioned as these studies were subjected to a wide range of substantial biases, including heterogeneity in the receptivity markers and demographics of the populations that were compared and the inability to control other confounding variables such as the adenomyosis, leiomyoma, endometrioma, hydrosalpinges, or endometrial polyp size, number and location. Despite limitations, this study has the potential to guide clinical practice for this challenging problem and direct future basic science and translational research. Clearly, well-designed prospective case-control studies are necessary to draw any conclusions about the relative impact of surgery on endometrium receptivity.

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