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REVIEW
ОБЗОРНАЯ СТАТЬЯ

Prediction of infertility in patients with uterine leiomyoma

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Abstract. Infertility is an important socio-economic problem due to the fact that planned childbearing occurs much later than three decades ago. In recent years, more attention has been paid to the role of uterine leiomyoma in the development of infertility. Uterine leiomyoma is a benign monoclonal, well-demarcated encapsulated tumor originating from the smooth muscle cells of the cervix or body of the uterus. Uterine leiomyoma is the most common uterine tumor in the reproductive age group, affecting 20—50 % of women. With conceptual changes in marriage and childbearing, the number of women over 35 with leiomyoma who want to have children has also increased significantly. The need to treat submucosal fibroids is widely recognized, but fibroids of other locations and sizes remain a clinical mystery. The purpose of the literature review was to determine the role of uterine fibroids in predicting infertility. It has been established that the incidence of uterine leiomyoma in women of reproductive age is on average about 40 %, infertility associated with this pathology occurs in 5—10 % of women. In 10 % of cases of infertility, uterine leiomyoma is the only established cause of infertility. Uterine leiomyoma is common among women of reproductive age, and as women continue to delay childbearing, an increasing number of patients will require fertility-preserving treatment options. Leiomyoma affects not only fertility but also obstetric outcomes. Women with intramural fibroids without cavity deformity have a 21 % reduction in live birth rates after in vitro fertilization compared with controls without fibroids. Despite advances in fundamental understanding of the biology of leiomyomas, the role of different fibroid variants remains a matter of discussion. The question of the negative impact of submucosal nodes on infertility today is not in doubt, and the effect of subserous and intramural nodes requires further study.

Key words: uterine leiomyoma, infertility, prediction, risk factors, submucosal, subserous, intramural nodes

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Introduction

The clinical guidelines define infertility as a disease characterized by the inability to achieve a clinical pregnancy after 12 months of regular intercourse without contraception due to an impairment of the subject's ability to reproduce, either individually or in conjunction with her partner [1]. The causes of infertility are varied, one of which is undoubtedly the uterine factor due to the presence of uterine fibroids. Leiomyoma of the uterus (Further—LU) defined as “a benign monoclonal, well-demarcated encapsulated tumor of smooth muscle cell origin of the cervix or uterine body” [2].

LU is the most common uterine tumor in the reproductive age group, affecting 20—50 % of these women and hence its association with infertility, although controversial, is always of great concern to both clinicians and patients [3].

Infertility, both primary and secondary, is a common occurrence in this disease; some studies have found that the incidence LU in women of reproductive age is up to 40 %, infertility associated with LU occurs in 5—10 % of women [4]. In other studies, primary infertility associated with LU is detected in 20—25 % of cases, secondary in 35—50 %. At the same time, the combination of LU with other factors of infertility is observed in 40—60 % of women [5]. In another study, LU is associated with 10 % of cases of infertility and is the only established cause of infertility in 1—3 % of patients [6]. At the same time, the role of LU in the development of infertility has not yet been determined, since there are numerous cases of pregnancy with a favorable outcome with multiple LU, even large ones [7].

Risk factors for uterine leiomyoma

Several risk factors for the disease have been identified, ranging from genetic predisposition to poor lifestyle habits [8].

Risk factors for developing LU include: race, age, lack of pregnancy and even delayed, early menarche, parity (protective effect), caffeine, alcohol, high blood pressure, obesity, genetic changes and others, such as a diet that includes an abundance of red meat, while smoking, possibly associated with a relative change in estrogen metabolism, reduces the risk of developing fibroids [9—10].

Symptoms and pathogenesis of uterine leiomyoma

In most cases, LU is asymptomatic, especially at the beginning of the development of the disease, with small sizes of nodes, a small number of them, which undoubtedly reduces the actual frequency of detection of this disease [11], all this against the background of a delayed first pregnancy, which in turn is a risk factor for the development of LU.

The purpose of the literature review was to determine the role of uterine fibroids in predicting infertility.

The solution of the researcher-task was carried out through analysis of corpora of scientific publications and discourse analysis, based on the definition of various mechanisms for the occurrence of such an ailment as infertility in women with uterine myoma.

Mechanisms of infertility development in uterine leiomyoma

Scientific interest in this issue is relevant and is described in many works of national and foreign scientists affecting genetics, epidemiology, hormonal aspects and molecular mechanisms of tumor development. However, there is no specific pathogenetic substantiation of the effect of LU on the reproductive function of women [12].

Analyzing this subject, it is impossible not to talk about the pathogenesis of infertility caused by LU. The beginning of everything is considered “hormonal changes that occur in a woman’s body due to changes in various departments of a single functional system: the hypothalamus-pituitary gland-ovaries-uterus. In 56—60 % of patients with LU, anovulatory cycles with varying degrees of estrogen saturation and / or biphasic menstrual cycles with luteal phase deficiency are detected [13]. In addition to hormonal disorders, there are other mechanisms for the development of infertility in LU.

Next, we consider some mechanisms of infertility development in LU.

The pathogenesis of infertility in LU is fairly well known and includes:

1. Mechanical factor (resistance to sperm, egg or embryo transport has been proposed as a mechanism to explain the effect of fibroids on fertility);

2. Dysfunctional myometrial injury (Cine MRI demonstrated accelerated mid-luteal peristalsis (defined as ≥ 2 peristaltic movements in 3 min) in the presence of intramural fibroids and reached a 40 % pregnancy rate in this population within 1 year after restoration of normal peristalsis by myomectomy);

3. Implantation disorders due to cytokine factors (decrease in the levels of certain cytokines, mainly IL-10 and glycodelin, in mid-luteal uterine lavages of women with submucosal fibroids) [3].

The effect of LU on fertility undoubtedly depends on its location [14].

Classification given by the International Federation of Gynecology and Obstetrics (FIGO) is of the greatest importance, since with this classification it is possible to

determine all variants of the pathogenesis of infertility due to LU.

There are a number of different mechanisms by which LU negatively affects fertility.

Mechanical factor. In addition to the fact that the promotion of spermatozoa in the uterine cavity is difficult, as well as the entry of the embryo through the fallopian tubes after fertilization, it has also been proven in a number of studies that LU leads to a change in the functional properties of the endometrium, a change in the architectonics of the endometrium with a violation of its implantation ability due to impaired blood circulation passing through the uterine arteries, LU also contributes to impaired endometrial receptivity, which determines endometrial dysfunction. According to Pritts et al. submucosal nodules causing intracavitary curvature were associated with a lower implantation rate than in LU women (3.0—11.5 % vs. 14—30 %) and an increased risk of early pregnancy loss (47 % vs. 22 %) [15,16,17]. A recent analysis has shown that submucosal, intramural, and subserous fibroids affect fertility differently, and they are mainly associated with submucosal lesions leading to implantation defects [18].

On the contrary, there is controversy as to whether LMs that do not cause distortion of the uterine cavity affect fertility. The influence of intramural and subserous nodes on the reproductive function of women remains a subject of discussion due to the inconsistency of two studies of the same year: Christopoulos G. et al. and Styer A.K. et al. [19, 20].

On the other hand, intramural fibroids in contact with the endometrium may have a very different effect on implantation than those in which the myometrium is located between the myoma and the endometrium. For example, a recent study using the FIGO classification system found that single or multiple type 3 leiomyomas ≥ 2 cm in diameter, alone or in combination, were associated with lower implantation rates as well as reduced rates of clinical pregnancy and delivery [21]. It should be emphasized that the presence of intramural and subserous myomas is associated with changes in uterine peristalsis and vascular blood flow, as well as impaired transport of spermatozoa and oocytes and embryo implantation [22]. It is worth noting that the

data show a 21 % reduction in live birth rates after in vitro fertilization (IVF) in women with intramural fibroids without cavity deformity compared to controls without fibroids [23].

Subserous fibroids, both sessile and pedunculated, that distort the outer contour of the uterus, do not appear to have a significant effect on fertility potential, despite the fact that the same study by Pritts et al. showed that the presence of fibroids, regardless of location, significantly reduced the incidence of implantation, clinical pregnancy, and current pregnancy/live birth, when the analysis was limited to subserous fibroids, no difference was observed for any of these endpoints. Therefore, subserous fibroids do not appear to affect fertility outcomes and their removal does not provide any benefit [24]. Other studies have shown that submucosal fibroids cause a blunted decidualization response with reduced release of cytokines important for implantation, such as leukocyte inhibitory factor and cell adhesion molecules [25].

Endometrial factor. This factor occupies one of the main places in the genesis of reproductive failures. “Optimal conditions for immersion of the ovum into the endometrium are noted during the “implantation window”, which corresponds to 6—10 days after the peak of luteinizing hormone (LH) in the blood, or 20—24 days of a 28-day menstrual cycle” [26]. Successful implantation is determined by a complex of structural and functional characteristics of the endometrium (genetic, proteomic and morphological), united by the term “Endometrial receptivity” [27].

The expression of genes encoding specific proteins reflects the essence of the genetic level of endometrial receptivity. The proteomic level includes: receptors for sex steroid hormones, various adhesion molecules, cytokines and growth factors that play a decisive role in the process of blastocyst implantation [26].

The results of the study show that LU causes vascular changes in the endometrium, and as a result, inflammation, which leads to the creation of an unfavorable environment for embryo implantation and, thus, to infertility [28].

Certain intrauterine cytokines in early pregnancy are believed to be responsible for implantation and early

embryonic development. Implantation is a complex process involving several factors such as HOXA-10, glycodelin, leukemia inhibitory factor and glutathione peroxidase 3 [29]. The exact cellular and molecular mechanisms that guide and control the development and growth of LU are not clearly understood. However, several factors have been implicated in the development and growth of LU, such as cytokines, chemokines, growth factors, extracellular matrix components, vasoactive substances, and miRNAs [30].

Cytokines are low molecular weight proteins that are produced and released by cells of the immune system, they regulate intercellular and intersystem interactions, determine cell survival, stimulation or suppression of their growth, differentiation, functional activity and apoptosis, and also ensure the coordination of the action of the immune, endocrine and nervous systems under normal conditions and in response to pathological influences.

Interleukins (hereinafter referred to as ILs) are a type of cytokines that were originally thought to be expressed only by leukocytes, but were later found to be produced by many other cells in the body. They play an important role in the activation and differentiation of immune cells, as well as in proliferation, maturation, migration and adhesion. ILs also have pro-inflammatory properties. Thus, the main function of IL is to modulate growth, differentiation, and activation during inflammatory and immune responses [31]. To date, many subclasses of IL are known; IL-10, which is an anti-inflammatory cytokine, the production of which is predominantly carried out by subpopulations of T cells or macrophages, plays a certain role in the pathogenesis of LU. IL-10 usually inhibits the activation of neutrophils and macrophages, which can be sources of IL-6 and TNF- α synthesis. In addition, several authors have described the unique ability of IL-10 to block cytokines and chemokines of macrophages activated by lipopolysaccharide (LPS), which can stimulate inflammatory processes [32]. Significant reductions in the levels of several cytokines, mainly IL-10 and glycodelin, have been reported in mid-luteal uterine lavages of women with submucosal fibroids.

Glycodelin is a progesterone-regulated glycoprotein secreted into the uterine cavity by secretory/decidualized endometrial glands and has properties such as angiogenesis stimulation and natural killer (NK) suppression. Glycodelin has three main isoforms that are found in different tissues and environments of the reproductive system, depending on the place of their production: amniotic fluid (glycodelin A), endometrium (glycodelin A), seminal plasma (glycodelin S) and follicular fluid (glycodelin F) [3].

Glycodelin is synthesized in the ovaries (follicle, corpus luteum), fallopian tubes, secretory endometrium, maternal part of the placenta, in men—in the seminal vesicles, this protein was found in endometriosis foci, extracts of malignant and benign tumors of the ovaries and uterus, in including LU. In the female reproductive tract, spermatozoa are exposed to glycodelin A and F, which inhibit the binding of spermatozoa to the zona pellucida. As spermatozoa migrate through the cumulus matrix, glycodelin F as well as glycodelin A-dependent inhibitory activity of gamete interaction is reduced due to the presence of a specific isoform of cumulus glycodelin, designated as glycodelin C, which has the effects of stimulating sperm binding to the zona pellucida [33]. There is also an opinion that the deficiency of glycodelin that develops with infertility of unknown origin indicates a failure of the “friend or foe system, as a result of which the spermatozoon can be perceived by the egg as a foreign cell” [34].

In addition to glycodelin’s “contraceptive” properties, it has been suggested that glycodelin is immunosuppressive by inhibiting natural killer (NK) cell activity. During implantation, glycodelin levels rise and may protect the embryo at the endometrial level from destruction of NK cells [35].

It is believed that the proliferative effects of estrogens and progesterone can be manifested through pro-inflammatory mediators: tumor necrosis factor α (TNF α), growth factors: transforming growth factor β (TGF- β), basic fibroblast growth factor (basic FGF), as well as inhibitors of apoptosis: cellular tumor antigen p53 (p53), apoptosis regulator bcl-2 (bcl-2) [36]. The HOXA10 gene also plays a certain role in the development of infertility in intramural and subserous

LM. The HOXA10 and HOXA11 genes and the protein products they encode are currently considered as one of the key regulators of endometrial receptivity during embryo implantation, which determine fertility in general [37]. HOXA-10 is responsible for cell differentiation while glycodelin is responsible for promoting angiogenesis, suppressing NK cells and inhibiting sperm binding to the zona pellucida, as already mentioned above. Typically, both factors decrease during the follicular phase and increase during implantation [29]. In an animal model, a decrease or absence of HOXA10 in the uterine endometrium leads to subfertility or infertility due to the inability of the embryo to implant, a study by Rackow and Taylor showed that HOXA10 is significantly reduced in submucosal fibroids compared with the control group, and although in patients with intramural myomas, there was a trend towards lower HOXA10 levels, this trend was not significant, in contrast, Matsusaki and colleagues showed a significant decrease in HOXA10 in patients with intramural fibroids compared with healthy controls [38], in another study of the effect of LU on the endometrium, using molecular markers of endometrial receptivity, a decrease in HOX gene expression was found throughout the endometrium, and not just over submucosal fibroids. This observation implies that impaired fertility may be due to a global effect, and not just a focal change in the endometrium that covers the fibroids [39].

In the presence of LU, both HOXA-10 and glycodelin were reduced at the time of implantation. Although the studies that have shown decreasing trends in HOXA-10 are not extreme, this decrease, which causes failure of embryo implantation, has been confirmed in an animal model. Thus, it is proposed that the reduction of both factors is the reason for the failure of embryo implantation, causing infertility [28].

Conclusion

LU is common among women of reproductive age, and as women continue to delay childbearing, an increasing number of patients will require fertility-preserving treatment options. It is worth emphasizing

that LU affects not only fertility, but also obstetric outcomes.

It is worth recognizing the progress made in the fundamental understanding of the biology of the LU. As already mentioned, the role of different variants of myomas remains a matter of debate. The question of the negative impact of submucosal nodes on infertility today is not in doubt, and the effect of subserous and intramural nodes requires further study.

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Прогнозирование бесплодия у пациенток с лейомиомой матки

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Аннотация. Бесплодие является важной социально-экономической проблемой, в связи с тем что запланированное деторождение происходит гораздо позже, чем три десятилетия назад. В последние годы все больше внимания уделяется

роли лейомиомы матки в развитии бесплодия. Лейомиома матки — доброкачественная моноклональная, хорошо отграниченная капсулированная опухоль, происходящая из гладкомышечных клеток шейки или тела матки. Лейомиома матки является наиболее распространенной опухолью матки в репродуктивной возрастной группе, поражающей 20—50 % женщин. С концептуальными изменениями в вопросах брака и деторождения число женщин старше 35 лет с лейомиомой, желающих иметь детей, также значительно увеличилось. Необходимость лечения подслизистых миом широко признана, но миомы других локализаций и размеров продолжают представлять собой клиническую загадку. Целью литературного обзора являлось определение роли миомы матки при прогнозировании бесплодия. **Выводы.** Установлено, что частота встречаемости лейомиомы матки у женщин репродуктивного возраста составляет в среднем около 40 %, бесплодие ассоциированной с данной патологией встречается у 5—10 % женщин. В 10 % случаев бесплодия лейомиома матки является единственной установленной причиной бесплодия. Лейомиома матки широко распространена среди женщин репродуктивного возраста, и поскольку, женщины продолжают откладывать деторождение, все большему числу пациентов потребуются варианты лечения, сохраняющие фертильность. Лейомиома влияет не только на фертильность, а также на акушерские исходы. У женщин с интрамуральными миомами без деформации полостей наблюдается снижение частоты живорождения на 21 % после экстракорпорального оплодотворения по сравнению с контрольной группой без миомы. Несмотря на прогресс, достигнутый в фундаментальном понимании биологии лейомиомы, роль различных вариантов миом остается предметом для дискуссии. Вопрос об отрицательном влиянии субмукозных узлов на бесплодие на сегодняшний день не вызывает сомнений, а влияние субсерозных и интрамуральных узлов требуют дальнейшего изучения.

Ключевые слова: лейомиома матки, бесплодие, прогнозирование, факторы риска, субмукозные, субсерозные, интрамуральные узлы

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