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HABITUAL MISCARRIAGE OF PREGNANCY IN WOMEN WITH HYPERPROLACTINEMIA

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Abstract*. Hyperprolactinemia is a common endocrine disorder, occurring in less than 1% of the general population. It can lead to a variety of reproductive health problems, including the risk of pregnancy complications such as habitual miscarriage. Recurrent pregnancy loss is a heterogeneous disorder affecting up to 2-5% of married couples.*
Keywords*: hyperprolactinemia; habitual miscarriage; prolactin; inhibin; pregnancy.*

Actuality. Hyperprolactinemia is a condition in which the level of prolactin in the blood serum is elevated. This type of pathology is the most common disorder of the hypothalamic-pituitary system and is one of the common causes of human reproductive dysfunction. The problem of prolactin disorders in modern conditions is of particular importance due to the prevalence of this pathology among women of childbearing age and many not always clear questions about the significance of prolactin in the physiology and pathology of the reproductive system of women [46,50,51].

Prolactin: Synthesis, secretion and biological role

The development of sensitive radioimmunological methods for measuring human prolactin has made it possible to study its biological properties in more detail, obtain information about its physiology and pathophysiology of secretion, and also identify its role in human life.

Prolactin (PRL) is a polypeptide consisting of 199 amino acids and containing three intramolecular disulfide bonds. It circulates in various forms - monomeric PRL (“little prolactin” 23 kDa), dimeric PRL (“big prolactin” 48-56 kDa) and macroprolactin (“big, big prolactin”, consisting of prolactin associated with immunoglobulins, >100 kDa) [35,47,48].

The monomeric form makes up 80-90% of the total prolactin content, the dimeric form is 10-15%, and about 5% is macroprolactin. Glycolyzed and non-glycolyzed forms of monomeric prolactin have also been isolated. The glycolyzed form of prolactin has a slightly larger molecular weight of 25 kDa [33,36,49].

The role of each prolactin isoform in humans is still being debated, and definitive conclusions on their specificity have not yet been established. Prolactin is synthesized by lactotrophs of the anterior pituitary gland, which constitute approximately 15-25% of all cells of the anterior pituitary gland. The number of these cells is the same in both sexes and does not change with age [3, 35,46]. In the early 90s of the last century, it was proven that a quarter (25%) of prolactin present in the blood is of extrapituitary origin [28]. Modern immunohistochemical methods have made it possible to detect the presence of prolactin in malignant tumors, intestinal mucosa, endometrium, decidua, granulosa cells, proximal tubules of the kidneys, and adrenal glands. The physiological role of ectopic prolactin production is not completely clear. [11,26,49]. PRL is secreted continuously, in basal and pulsatile secretion modes. The secretion rate of prolactin ranges from 200 to 536 mcg/day/m2, and the half-life is from 25 to 50 minutes. The basal level of prolactin in women averages 13 ng/ml, in men - 5 ng/ml. During the day, against the background of basal prolactin production, only 13-14 peaks of secretion are observed with an

interval of 1.5-2 hours. The highest level of the hormone is observed during deep sleep and early morning, and the lowest in the evening. Peak plasma concentrations of prolactin occur between 4:00 and 6:00 am. PRL is metabolized in the liver (75%) and kidneys (25%) [35,38,45].

Prolactin affects almost all organs and tissues of the body, i.e. is a multifunctional hormone. To date, more than 300 biological effects of prolactin have been identified. The main role of prolactin is to stimulate the process of milk synthesis and maintain lactation in the postpartum period. Other effects of BPD [31,32,33,47,49]:

1. Inhibition of the secretion of gonadotropin-releasing hormone (GnRH), which leads to hypogonadotropic hypogonadism;

2.Improves glucose homeostasis by increasing β-cell mass under certain conditions;

3. Enhances the secretion of dihydroepiandrosterone (DHEA), cortisol and aldosterone by adrenal cortex cells;

4.Acts as a cytokine and plays an important role in human immune responses. The effects of PRL on immunological systems may be concentration dependent, resulting in immunostimulation at moderate levels and inhibition at high levels;

5.Participates in osmoregulation, increasing the absorption of water and salts in all segments of the intestine and reducing renal excretion of Na+ and K+;

6. Stimulates proliferation, differentiation and migration of neuronal stem cells;

7. Psychotropic effect on behavioral reactions, etc.

Hyperprolactinemia

In clinical practice, doctors often encounter pathology caused by increased levels of prolactin. This is a relatively young problem, since only in 1971 a radioimmunological method for determining prolactin in humans was proposed. In the literature one can find an ambiguous approach to the interpretation of the term “hyperprolactinemia”, to normal and pathological prolactin levels, rules for diagnosis, indications for therapy, etc. [45,49]. One of the reasons for such disagreements is due to the fact that patients with hyperprolactinemia are treated by doctors of different specialties - endocrinologists, gynecologists, neurosurgeons, who, accordingly, have different views on the problem and their approach to the management of such patients. Another reason is related to the imperfection of commercial kits for determining prolactin levels. Thus, there was a need to develop tactics for coordinated actions among doctors of various specialties [45]. The first consensus recommendations for the diagnosis and management of prolactin in clinical practice were proposed at the 9th International Pituitary Congress in 2005, which was held in San Diego (USA). These recommendations were subsequently supplemented and modified by the consensus of the French Society of Endocrinology and practical clinical guidelines for the diagnosis and treatment of hyperprolactinemia prepared by the International Society of Endocrinology in 2011 [22,46].

Epidemiology: Hyperprolactinemia occurs in less than 1% of the general population, 5-14% of patients with secondary amenorrhea, 40 to 70% of women presenting for infertility, and 12 to 36% of women suffering from miscarriage [38]. The most common type is prolactin-secreting tumor (prolactinoma), which accounts for up to 40% of all clinically recognized pituitary adenomas [3]. According to various authors, the prevalence of hyperprolactinemia is about 10 per 100,000 in men and 30 per 100,000 in women, respectively, and it is the second most common cause of infertility in women [35].

Etiology. Hyperprolactinemia can be physiological or pathological. Some of the common causes are listed in (Table 1) [4,18,41].

Table No. 1.

Causes of hyperprolactinemia

Physiologic: Pregnancy; lactation; stress; sleep; coitus; exercise, etc.
Pathologic: 1. Systemic diseases – primary hypothyroidism; adrenal insufficiency; polycystic ovary syndrome (?); renal insufficiency; cirrhosis; pseudocyesis; epileptic seizures 2. Hypothalamic diseases – tumors (craniopharyngiomas, dysgerminomas, meningiomas, etc.); infiltrative disorders (histiocytosis, sarcoidosis, etc.) metastasis; cranial radiation; Rathke's cleft cysts, etc. 3. Pituitary diseases – prolactinomas; acromegaly; thyrotropinomas; Cushing's disease; infiltrative disorders; metastasis; hypophysitis; empty sella syndrome, etc. 4. Stalk disorders – inflammatory (hypophysitis; granulomatosis with polyangiitis (Wegener's), sarcoidosis, Langerhans cell histiocytosis) and infectious (tuberculosis) lesions; neoplasms (germinomas); traumatic brain injury 5. Neurogenic – chest wall lesions (burns; breast surgery; thoracotomy; nipple rings; herpes zoster; etc.); spinal cord injury (cervical ependymoma; tabes dorsalis; extrinsic tumors; etc.), breast stimulation, etc. 6. Idiopathic 7. Ectopic prolactin production – renal cell carcinoma; ovarian teratomas; gonadoblastoma; non-Hodgkin lymphoma; uterine cervical carcinoma; colorectal adenocarcinoma, etc. 8. Macroprolactinemia
Pharmacologic Antipsychotics Antidepressants Antihypertensive drugs (verapamil; α-methyldopa) Prokinetic agents (metoclopramide; domperidone) H2-receptor blocker agents Others (estrogens; anesthetics; opiates; methadone; morphine; etc)

Physiological hyperprolactinemia is transient and adaptive, and is usually mild or moderate [21]. When all pathological causes of increased prolactin are excluded, a diagnosis of idiopathic hyperprolactinemia is established. It should be emphasized that an increase in prolactin levels in the absence of clinical manifestations is often explained by the phenomenon of macroprolactinemia (12.5-40%) [13].

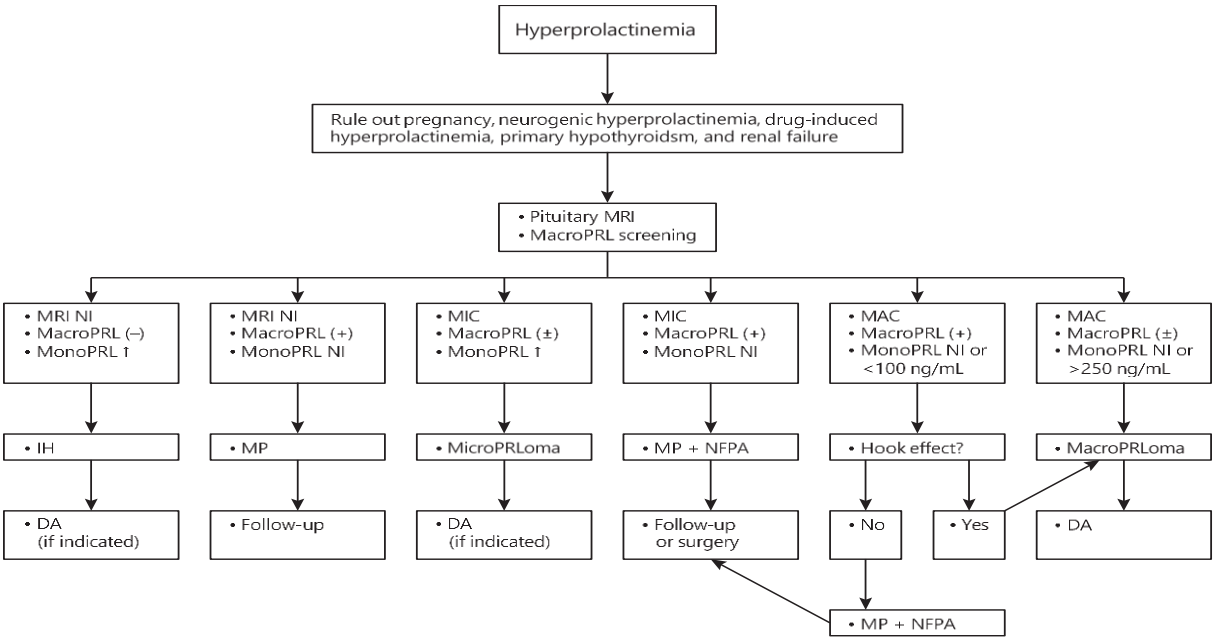
In 60% of cases, hyperprolactinemia is caused by lactotrophic adenomas—prolactinomas, which account for about 40% of all hormonally active pituitary adenomas. Based on their size, prolactinomas are classified into micro (up to 10 mm) and macroprolactinomas (10 mm or more). As a rule, microadenomas are associated with a prolactin level of more than 2000 mU/l, macroadenomas - more than 5000 mU/l. A prolactin level of less than 2000 mU/L is more typical for hyperprolactinemia of non-tumor origin [13].

Clinical picture. Regardless of the cause of hyperprolactinemia, excessive secretion of prolactin leads to disturbances in the rhythm of LH and FSH secretion and, as a consequence, to

hypogonadism and infertility. On the part of the reproductive system in women, galactorrhea, menstrual irregularities (amenorrhea, oligomenorrhea, opsomenorrhea, anovulatory cycles, luteal phase insufficiency), early miscarriage, infertility, and decreased libido are observed. In men, manifestations of hyperprolactinemia can be a decrease or absence of libido and potency, infertility, and gynecomastia [13].

Diagnostics. Determining the etiology of hyperprolactinemia often poses a major challenge for clinicians. An appropriate assessment is necessary to provide the most appropriate treatment. The proposed algorithm for assessing hyperprolactinemia is illustrated in (Table 2) [4].

Evaluation of hyperprolactinemia. Table 2.



NI, normal; MacroPRL, macroprolactin; IH, idiopathic hyperprolactinemia; MIC, microadenoma; MP, macroprolactinemia; MonoPRL, monomeric prolactin; MAC, macroadenoma; MicroPRLoma, microprolactinoma; ↑, high; MacroPRLoma, macroprolactinoma; NFPA, nonfunctioning pituitary adenoma; DA, dopamine agonist; –, negative; +, positive; ±, positive or negative.

Hyperprolactinemia and pregnancy

In the structure of neuroendocrine disorders occurring in pregnant women, hyperprolactinemia occupies one of the main places. The prevalence of this pathology in the population is 0.5%; elevated prolactin levels are observed on average in every fifth patient with infertility [16].

It should be emphasized that during pregnancy the level of prolactin increases significantly - up to 200-400 ng/ml, i.e. 10-20 times. In this regard, there is a certain risk of a symptomatic increase in prolactin levels during pregnancy [23].

Pregnancy in patients with hyperprolactinemia occurs with characteristic complications and has its own characteristics [5,6,17,33]:

• In the first trimester there is a high risk of miscarriage (48.4%, in healthy people 15%), spontaneous abortion (16.1%). In sick pregnant women, cessation of embryo development is observed at 6-7 weeks of gestation. Noteworthy is the extremely high frequency of undeveloped pregnancies, amounting to 80% of the total number of spontaneous terminations of short-term pregnancies in patients with initial hyperprolactinemia.

• In the second trimester of pregnancy, the frequency of threatened miscarriage at various times also increases (40.3%). The high frequency of spontaneous abortion at various times is explained by a decrease in progesterone secretion during hyperprolactinemia.

• In the third trimester, there is a high incidence of edema (45%), premature birth (11.8%), and placental insufficiency.

• According to ultrasound data, 47% of patients with hyperprolactinemia show signs of premature maturation of the placenta, hemodynamic disturbances in the aorta and middle cerebral artery of the fetus. Signs of chronic fetal hypoxia are detected according to cardiotocography in 39% of cases.

• The course of labor has the following features: untimely rupture of amniotic fluid (47.4%), weakness of labor (36.8%), acute fetal hypoxia (7.9%).

Summarizing the main results, it is necessary to emphasize that hyperprolactinemia syndrome during gestation should be considered from the perspective of a possible risk of developing obstetric and perinatal pathology. One of them is recurrent miscarriage.

Recurrent pregnancy loss (RPL)

RPL is a complex health problem with no generally accepted definition. Inconsistency in definitions concerns not only the number of spontaneous abortions (two or three) taken for recurrent miscarriage, but also the types of pregnancy and gestational age at miscarriage. Table 3 shows a comparison of the definitions used for PNB in the RCOG, ASRM and ESHRE guidelines [7,10,27,30].

Table No. 3

Summary of definitions of recurrent pregnancy loss used in various guidelines

Parameter	RCOG 2011	ASRM 2012	ESHRE 2017
Pregnancy	All pregnancy losses not otherwise specified	Clinical pregnancy determined by ultrasound/histological examination	Serum/urine human chorionic gonadotropin (hCG) + ectopic/molar pregnancy is not included in the definition
Weeks of pregnancy	Up to 24 weeks	It only mentions that most are lost before the 10th week.	Up to 24 weeks
Repetition	3	2	2
Consistent	Consistent	Consistent	Consistent or inconsistent

Almost 10–15% of clinical pregnancies and 30% of all pregnancies end in spontaneous abortion, making it the most common complication of pregnancy.

Differences and inconsistencies in definitions of RPL lead to difficulties in estimating true prevalence. Based on available sources, it is estimated that about 5% of women can experience two or more miscarriages in a row and only 0.4–1% have three or more miscarriages. The risk of spontaneous abortion in women after a previous single miscarriage is 12–20%. After two miscarriages, the risk increases to 29%, and after three - to 36% [40]. The incidence of incidental RPL in women in the 20–24 age group is 0.13%, compared with an approximately 100-fold increase in the 40–44 age group (13.3%) [10].

RPL is a polyetiological disease, the cause of which is often unknown. Several factors have been suggested to contribute to the pathogenesis of RPL, including maternal age (9–75%), endocrine diseases (17–20%), uterine morphological abnormalities (10–15%), chromosomal abnormalities (2–8%), thrombophilia ., infectious agents (0.5–5%) and autoimmune diseases (20%). However, in approximately 50–75% of cases of RPL, the exact cause is not clear and therefore remains unexplained (idiopathic) [40]. Endocrine disorders play a significant role in approximately 12–20% of RPL. Although systemic maternal endocrine diseases such as diabetes mellitus and thyroid disease are associated with spontaneous abortion, RCOG guidelines suggest that “well-controlled diabetes is not a risk factor for recurrent miscarriage [30,40].

Because progesterone plays an important physiological role in successful implantation and pregnancy, insufficient progesterone levels (i.e., luteal phase deficiency) are thought to be associated with spontaneous pregnancy loss [40]. Polycystic ovary syndrome (PCOS) is not considered a prognostic factor for RPL. However, obesity alone or associated with PCOS increases the risk of recurrent miscarriage. Recent studies have shown that obesity in women with a previous history of RPL increases the risk of recurrent miscarriage [40].

The exact mechanism of the endocrine genesis of pregnancy loss due to hyperprolactinemia, which is more common at the age of 25–40 years, has not been fully studied. Hyperprolactinemia contributes to insufficient preparation of the endometrium for pregnancy and defective implantation of the fertilized egg, and has a pathological effect on the production of gonadotropic hormones and the function of the corpus luteum [43]. The role of hyperprolactinemia in the genesis of female infertility is unambiguous and does not raise questions, in contrast to information about its effect on RPL, which remains controversial and insufficient. However, the relationship between hyperprolactinemia and RPL is controversial [44]. In a case-control study, Bussen et al. [44,50] assessed the incidence of endocrine disorders during the follicular phase in women with a history of RPL. The concentration of prolactin in the main group of 42 women with RPL (three or more consecutive miscarriages) was significantly higher compared to the control group (42 nulliparous women with tubal or male factor infertility without miscarriage) ($p = 0.015$). They concluded that RPL is associated with impaired prolactin secretion during the follicular phase [27]. However, despite the large number of studies devoted to the study of this pathology, many aspects of this problem remain unstudied, in particular, the effect of hyperprolactinemia in women with recurrent miscarriage on the course and outcome for the mother and fetus.

Of undoubted interest is the question of what laboratory parameters precede spontaneous termination of short-term pregnancy in patients with hyperprolactinemia [36]. Along with an increase in the concentration of hyperprolactinemia in patients with a terminated pregnancy, there is a marked decrease in the serum concentrations of placental lactogen (PL), progesterone (P) and trophoblastic glycoprotein (TBG). As for the serum levels of human chorionic gonadotropin (hCG), inhibin A and α 2 microglobulin of fertility (AMGF), in pregnant women with spontaneous

abortion there is only a tendency to their decrease [36]. In recent years, thanks to scientific advances, new data has increasingly become available, allowing not only the development of new methods for diagnosing and treating infertility, but also preventive measures. Particularly noteworthy in this regard are studies devoted to the new family of TGF proteins involved in the pathogenesis of the development and outcomes of endocrine RPL and infertility. The transforming growth factor β (TGF-β) superfamily includes the hormones inhibins, activins, and anti-Mullerian hormone. All members of this family are dimeric glycoproteins involved in the regulation of tissue growth and differentiation [1].

Inhibins and activins

Inhibins and activins are closely related peptides secreted by various organs, including the pituitary gland, ovaries and testes, as well as the placenta. These peptides affect the function of gonadotrophs: inhibins suppress the function of gonadotrophs, and activins stimulate it [1,25,37]. Inhibin is a glycoprotein heterodimer with a molecular weight of 32 kDa, and activin is a glycoprotein heterodimer with a molecular weight of about 25 kDa. The inhibin molecule is formed by two dimers: the same α-subunit (20 kDA) and two different β-subunits - βA and βB (13 kDA), connected by disulfide bridges. As a result, two isoforms of inhibin are formed: inhibin A, which consists of α- and βA-subunits (αβA heterodimer), and inhibin B, consisting of α- and βB-subunits (αβB heterodimer) [1,25,37,42] .

Inhibin and activin were thought to act exclusively on the pituitary gland in a classic endocrine feedback loop, but these factors have since been described in a large number of other tissues, namely the placenta, pituitary gland, adrenal gland, bone marrow, kidney, spinal cord and brain , making it likely that they have more diverse biological actions [1,2]. The corpus luteum is the main site of inhibin production during the luteal phase of the human menstrual cycle. There is conflicting evidence regarding the source of inhibin production in early pregnancy. Trophoblast has been shown to express messenger RNA inhibin α and β subunits using Northern blot analysis [24]. Immunohistochemistry has demonstrated the production of immunoreactive (IR) inhibin by trophoblasts, and cell culture studies have also demonstrated that placental cytotrophoblast produces IR-inhibin. McLachlan et al [24] reported that levels of ir-inhibin in the maternal circulation were similar in women with functional ovaries and in women receiving donor eggs and therefore concluded that inhibin production was predominantly from the placenta. Ovarian granulosa cells are the main source of inhibins, activins and activin-binding protein (follistatin), while germinal (ogonia, oocytes) and somatic (theca, granulosa, luteal) cells express activin receptors, signaling components and inhibin coreceptors (betaglycan) [1,15]. Activins are involved in various functions within the ovary, including germ cell survival and primordial follicle assembly; follicle growth from preantral to midantral stages; suppression of thecal androgen production; stimulation of granulosa cell proliferation, FSH and CYP19A1 expression; increasing the ability of oocyte development; delayed luteinization of follicles and/or atresia and participation in luteolysis [1,2,42]. Inhibins (primarily inhibin A) are produced in greatest quantities by preovulatory follicles (and the corpus luteum in primates) and suppress FSH secretion through negative endocrine feedback [1,24]. Together with follistatin, inhibins act locally to antagonize auto-/paracrine activin (and BMP) signaling, thereby modulating many of the above processes. The balance between activin and inhibin shifts during follicle development, with activin signaling predominant in earlier stages but decreasing as inhibin and betaglycan expression increases [14].

Inhibins are glycoprotein hormones that have two molecular forms: inhibin A and inhibin B [1]. Inhibin is known to have a negative feedback effect on pituitary follicle-stimulating hormone secretion. The fetoplacental unit produces inhibin throughout pregnancy. Inhibin A is the predominant molecular form of inhibin in the maternal circulation from 4 weeks of pregnancy. Although the exact biological function of inhibin A during pregnancy is unclear, it is clear from recent studies that inhibin A may be a better marker of placental function than human chorionic gonadotropin due to its shorter half-life [2]. Possible clinical applications of measuring inhibin A in early pregnancy may include the prediction of miscarriage, Down syndrome, preeclampsia, and fetal growth restriction in the first and/or second trimester before the onset of clinical symptoms [9]. The source of inhibins, factors controlling inhibin production, possible functions of inhibin, and the use of inhibin measurement in normal and high-risk pregnancies are reviewed [1].

Starting from early pregnancy, the levels of mRNA of αβA and αβB subunits of inhibin gradually increase, reaching maximum values in the third trimester [24]. At the end of the menstrual cycle, during decidualization and in early pregnancy, the expression of inhibin α-subunit mRNA shifts from epithelial cells to stromal cells [14,15].

It has been established that decidualized human endometrial cells in culture respond to the introduction of activin A by increasing the secretion of matrix metalloproteinase 2, and inhibin A blocks this activin-mediated response [15]. Increased secretion of inhibin α-subunit mRNA by stromal cells correlates with the level of betaglycan mRNA in decidual tissue [14, 15]. It is known that the main source of inhibins during pregnancy is the fetoplacental complex. Inhibin can be produced by both cytotrophoblast and syncytiotrophoblast. In contrast to the low levels of inhibin A produced in the non-pregnant uterus, placental syncytiotrophoblast cells actively produce inhibin A along with betaglycans [8,14,15]. The exact role of inhibins in the placenta is unclear. A number of observations prove that inhibins and activins can play an important role in the regulation of the secretion of human chorionic gonadotropin and steroids by the placenta and participate in the pathogenesis of some disorders of its function, while inhibin is a powerful antagonist of the stimulating effect of activin [8, 15]. The concentration of inhibin A in the earliest stages of pregnancy is significantly higher than in non-pregnant women. It is assumed that in the very early stages of pregnancy, inhibin A is synthesized by cells of the corpus luteum [39]. It then begins to be secreted by cells of other tissues, such as the placenta. Increased secretion of inhibin A by extragonadal tissues may be the main reason for the suppression of FSH production by the pituitary gland during pregnancy. The level of inhibin A can be determined in the blood of a pregnant woman already on the ninth day after the release of the oocyte, and its appearance coincides with an increase in the level of human chorionic gonadotropin. By the 8th–10th week of pregnancy, the level of inhibin A rises to a maximum, and from the 14th to the 20th week it begins to decrease and a plateau phase begins, after which its level slowly increases again, and then there is a sharp rise in the third trimester [24]. The dynamics of inhibin A content suggests that its first peak reflects the function of the corpus luteum, and its further increase reflects the function of the rapidly growing placenta [15]. The level of inhibin B remains unchanged throughout pregnancy [1]. After birth, inhibin disappears from the mother's serum during the first 24 hours [24]. Inhibin as a marker of pregnancy complications

From the early stages of pregnancy, the level of inhibin A gradually increases, while the level of inhibin B remains low throughout its entire duration. In this regard, the level of inhibin A is used as an important and promising marker for diagnosing pregnancy complications [2].

According to a number of studies, early termination of pregnancy is preceded by a decrease in the level of inhibin A. There is evidence that the level of inhibin A in the first trimester of pregnancy is significantly lower in women with recurrent miscarriage than in healthy pregnant women [20,34]. The concentration of inhibin A may be more informative than the level of human chorionic gonadotropin (hCG) on the 11th day of embryo transfer in IVF cycles for predicting preclinical abortion after IVF [2,12]. These data allow the use of inhibin A levels as an early marker of the risk of miscarriage.

The level of inhibin A can also be used as a marker of the presence of remnants of the fertilized egg and placental tissue in the uterine cavity after spontaneous abortion. An increased level of inhibin A is a sign of incomplete abortion, while a sharp decrease in the level of inhibin A after spontaneous abortion can be considered as a marker of the absence of residual fetal tissue in the uterine cavity and, therefore, makes it possible not to perform curettage of the uterine cavity [2,19]. Thus, determining the level of inhibin A in women with spontaneous miscarriage will reduce the number of unnecessary intrauterine interventions. Data have been obtained on a lower level of inhibin A in the blood of women with ectopic pregnancy compared to this indicator in women with intrauterine pregnancy [2,29,34], which may indicate the participation of inhibins in the processes of transport and implantation of the embryo. When carrying out immunohistochemical analysis of syncytiotrophoblast villi obtained from women with complete and incomplete hydatidiform mole and from women with conventional abortion, a multiple increase in the expression of the α-subunit of inhibin was shown in cases of complete hydatidiform mole, which could possibly be a useful addition to the differential diagnosis of complete and incomplete hydatidiform mole [9]. These examination methods may facilitate the early identification of patients at higher risk of adverse outcomes that require close monitoring [2].

Conclusion

According to the data presented, increased prolactin levels during pregnancy are associated with the risk of developing RPL. Inhibin A can be used as a marker to assess the likelihood of complications during pregnancy.

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