

# Complications of Hyperprolactinemia During Pregnancy

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**Abstract** Among the various neuroendocrine disorders that occur in pregnant women, hyperprolactinemia syndrome is of great scientific and practical importance.

**Keywords** Prolactin, Hyperprolactinemia, Pregnancy, Pituitary tumors

## 1. Introduction

The problem of hyperprolactinemia during pregnancy: in 80% of cases, the syndrome in question occurs in young women aged 25-40 years (Naoki Hattori, 2013). Hyperprolactinemia is observed in pituitary tumors up to 45% of their total number, up to 40% in the idiopathic version. A certain influence on the frequency of this pathology of unfavorable environmental conditions cannot be ruled out. In addition, there is an increase in the frequency of hypothyroidism in women of reproductive age to 4-5%, as one of the main factors in the development of symptomatic hyperprolactinemia.

The causes of hyperprolactinemia are varied. These include both organic (micro- and macroprolactinomas, mixed somatotropinoprolactin adenoma of the pituitary gland, etc.) and functional factors (idiopathic hyperprolactinemia, stress, neuroinfections, primary hypothyroidism, dys hormonal diseases of the mammary glands, polycystic ovaries, pathology of the liver and kidneys, long-term use of medications, etc.) [1-3].

## 2. Materials and Methods

The pathogenetic mechanisms for the development of hyperprolactinemic hypogonadism are also diverse: a decrease or absence of the inhibitory effect of dopamine; stimulating effect of thyrotropin-releasing hormone; impaired secretion of both estrogens and androgens; the influence of melatonin, serotonin, catecholamines, prostaglandins on the secretion of PRL with the formation of lactotroph hyperplasia. The works of domestic and foreign authors confirm the presence of complex biochemical processes occurring in the neuroendocrine system in patients with hyperprolactinemia [4-6].

Hyperprolactinemia syndrome, which in most cases leads to the development of hyperprolactinemic hypogonadism, has also been the subject of extensive research over the past

30 years. Taking into account the pronounced influence of hyperprolactinemia on the reproductive system, priority has always been given to the study of disorders of the generative sphere, which determined that the features of the development and pathophysiology of osteopenic syndrome in this pathology are poorly understood. The study of osteopenic syndrome in hyperprolactinemia is complicated by the variety of etiological factors that cause pathological hyperprolactinemia (pathology of the hypothalamus; pathology of the pituitary gland; the presence of systemic diseases; pharmacological influences).

One of the complications of hyperprolactinemia is impaired mineralization of bone tissue (osteopenia or osteoporosis), which is explained by a deficiency of sex hormones (estrogens in women or androgens in men) and the direct effect of prolactin on bone. A significant decrease in bone mineral density (BMD) in the distal radius in women with hyperprolactinemia was first reported in 1980 [7-9]. Taking into account the variety of causes of hyperprolactinemia, data on the incidence of bone tissue pathology vary widely. So, according to the results of various studies, a decrease in bone mineral density with hyperprolactinemia is detected in 18 to 70% of cases [2-14], while in healthy women in perimenopause it is observed only in 10-12%. There is an opinion that in the absence of treatment, the rate of decrease in bone density can reach 3.8% per year [15-16]. It has been noted that a more pronounced decrease in bone mineral density is observed in young girls (16-18 years old) with hyperprolactinemia, which may be due to their failure to reach peak bone mass [15,17,18,19].

At the same time, in patients, even when normoprolactinemia is achieved, bone mineral density does not return to normal, which requires the doctor to more carefully monitor and prescribe in addition to dopamine agonists and anti-osteoporotic drugs [19-20]. It is traditionally believed that a decrease in the production of sex hormones is of primary importance for the development of osteopenic syndrome in HP. An increased level of prolactin, regardless of the reasons that caused it, suppresses the hypothalamic-pituitary-gonadal system, disrupts the cyclic secretion of gonadolibrins and

gonadotropins [21], reduces the frequency and amplitude of luteotropic hormone secretion, inhibits the effect of gonadotropins on the gonads, resulting in a decrease in the secretion of sex steroids (estrogen in women and androgens in men) and hypogonadism syndrome develops. The mechanisms of the influence of sex hormones on bone tissue are due to the presence of specific receptors on osteoblasts for estrogens and androgens, which makes the spongy substance of bone tissue a target organ for sex hormones.

Historically, among the risk factors for AP in women, the most significant is considered to be a deficiency of sex steroids (estrogens) [15,22]. Assessing the state of the calcium-regulating hormone system in HP is complicated by the difficulty of identifying one pathogenetic manifestation: HP is accompanied by hypogonadism, i.e. hypoestrogenism, which determines the complex effect. It has been proven that osteoclasts have receptors for estrogen, the latter suppress the synthesis of some lysosomal enzymes in osteoclasts, block the action of many osteoclast-stimulating factors (interleukins 1 and 6; tumor necrosis factor, etc.), stimulate the synthesis of osteoclastic inhibitory factors (transforming growth factor), osteoprotegerin. Therefore, a decrease in serum estrogen levels leads to an increase in bone resorption and, consequently, an increase in the serum level of the C-isomer of type 1 collagen telopeptide ( $\beta$ -CrossLaps or CL) [19,23]. The direct effect of estrogens on cells of the osteoblastic series, due to the presence of receptors for this hormone in the latter, ensures the synthesis and secretion of type 1 procollagen, non-collagen proteins, and differentiation of osteoblasts. In addition, there is evidence that estrogens reduce the sensitivity of bone tissue to parathyroid hormone and stimulate the synthesis of vitamin D3 in the kidneys [7,14].

Particularly significant are modern works devoted to the study of the effect of excess prolactin on disorders of the immune status. Prolactin has a large number of biological effects; one of the most important is its participation in the synthesis of progesterone by the corpus luteum of the ovaries. An increase in prolactin levels leads to damage to various levels of the hypothalamic-pituitary-ovarian system. The combination of hyperprolactinemia with diabetes mellitus, hypothyroidism, and hyperandrogenism aggravates the feto-placental relationship. There are currently no studies examining this issue.

### 3. Purpose of the Study

To study the features of the course of pregnancy in patients with hyperprolactinemia syndrome.

### 4. Study Materials and Methods

In accordance with the main purpose of the study, to solve the set tasks, a comprehensive clinical and laboratory examination was carried out to study the course of pregnancy, as well as the main indicators of the function of the

fetoplacental system in 74 patients of reproductive age with hyperprolactinemia syndrome. All 74 patients with hyperprolactinemia, depending on the genesis of this endocrine pathology, were divided into 2 main groups: Group 1 (n=32) - patients with hyperprolactinemia caused by the presence of prolactinoma of the pituitary gland; Group 2 (n=42) - women with idiopathic hyperprolactinemia. The control group consisted of 20 healthy pregnant women with normal levels of prolactin in the blood serum (the hormone was determined before pregnancy).

## 5. Study Results

Among the complaints made by patients with hyperprolactinemia syndrome before pregnancy, the main complaints were headache (40.3%), menstrual irregularities (85.5%), primary or secondary infertility (61.3%), galactorrhea (80.6%). The average age of pregnant women did not differ significantly between groups and was  $28.5 \pm 2.56$  years in the main group,  $27.6 \pm 2.69$  in the comparison group,  $27.1 \pm 2.42$  years in the control group ( $p > 0.05$ ). At the same time, there is a tendency for a larger number of women over 30 years of age in the main group - 16 (32%) people compared to 10 (22.2%) in the second group ( $p > 0.05$ ).

The average duration of the disease before pregnancy in women of the main group was  $4.23 \pm 0.53$  years, in women of the comparison group -  $2.77 \pm 0.38$  years ( $p < 0.05$ ), which determined the long duration of existence of hypothalamic-pituitary dysfunction. ovarian system and a less favorable background for pregnancy in the main group.

At the pregestational stage, analysis of prolactin (PRL) levels by group revealed significant differences in the initial level ( $p < 0.05$ ). In the main group before treatment -  $2510 \pm 256.1$  mIU/l, during treatment -  $559 \pm 51.2$  mIU/l; in the comparison group -  $1779 \pm 183.2$  mIU/l and  $444 \pm 39.8$  mIU/l, respectively.

In the main group, there was a high prevalence of concomitant endocrine syndromes - hypothyroidism (30%, vs 15% in the second group), AIT (40%, vs 25% in the second group), GDM (10%, vs 5% in the second group). Moreover, in the main group there were 6 (30%) cases of simultaneous combination of hyperprolactinemia, hypothyroidism and hyperandrogenism, while in the second group there were no such combinations.

During the study, women in the study groups were found to be highly burdened with somatic and gynecological diseases even before the onset of real pregnancy. The frequency of childhood infectious diseases (scarlet fever, mumps, influenza, measles, rubella, etc.) in 27 (54%) patients of the main group, in 19 (42.2%) of the comparison group and in 6 (20%) of the control group ( $p_{1:k} < 0.01$ ,  $p_{2:k} < 0.05$ ). These data are consistent with ideas about the role of respiratory infections in damage to the diencephalic region with subsequent disintegration of the activity of the hypothalamic-pituitary-gonadal complex (Kokolina V.F., 2001; Manukhin I.B., Tumilovich L.G., Gevorkyan M.A., 2001).

Pathology of the circulatory system (vegetative-vascular dystonia, hypertension) prevailed in groups of pregnant women with hyperprolactinemia and amounted to 18 (36%) cases in the main group, 14 (31.1%) in the comparison group and 5 (16) cases in the control group. .6%) ( $p>0.05$ ). A high incidence of liver and digestive system diseases was noted, which was detected in 28 (56%) women of the main group, 15 (33.3%) women of the comparison group and 6 (20%) of the control group ( $p<0.01$ ). Diseases of the kidneys and urinary system were detected in 17 (34%) women of the main group, 9 (20%) of the comparison group and 3 (9.9%) of the control group ( $p<0.05$ ). At the same time, there are significant differences ( $p<0.05$ ) in the prevalence of liver diseases in the subgroup with combined endocrine pathology (75%, vs 43.3% in the subgroup without combined endocrine pathology), which determines more pronounced metabolic changes in conditions of combined endocrine pathology.

A feature of pregnant women in the main group was the multiple nature of concomitant extragenital pathology, so 3 diseases or more were noted in 26 (52%) cases in the main group and in 15 (33.3%) cases in the second group ( $p>0.05$ ), which, perhaps indicates the activation of organ-organ mechanisms in the presence of a tumor substrate for the development of hyperprolactinemia.

When analyzing the characteristics of the gestational process in the first trimester in pregnant women with hyperprolactinemia, a high frequency of threatened miscarriage was established (in the main groups - 48.4%, in the comparison group - 15%;  $p<0.05$ ). Along with this, in contrast to the comparison group, patients with hyperprolactinemia syndrome experienced spontaneous termination of pregnancy (mainly at 6-7 weeks of gestation) in 16.1% of cases. The relatively high frequency of undeveloped pregnancies was noteworthy (80% of the total number of spontaneous abortions in the early stages). It should also be emphasized that the rate of miscarriage in patients of group 1 exceeded the same indicator in patients of group 2 (24.2% and 6.9%, respectively;  $p>0.05$ ).

The course of pregnancy with hyperprolactinemia of various origins is complicated by: toxicosis of the first half of pregnancy in 42% of cases in the main group and in 37.7% in the second group; threatening premature birth in 44% and 20%, respectively; gestosis - in 64% and 69%, respectively, placental insufficiency in 88% and 84% (in a subcompensated form - in 26% and 26.6%, respectively). The incidence of gestosis (mainly in the form of edema of pregnant women) in groups with hyperprolactinemia was significantly higher than in the control group: in the main group - 32 (64%) cases, in the comparison group - 31 (68.8%) compared to 12 (40%) in the control group ( $p<0.05$ ). In all study groups, a mild form of gestosis predominated. We found early manifestations of signs of gestosis in groups with hyperprolactinemia compared to the control group: in the period of 22-27 weeks of pregnancy, 13 (26%) cases were identified in the main group, in the comparison group - 13 (28.8%) compared with 3 (10%) cases in the control group ( $p<0.05$ ).

Fetal growth retardation syndrome was diagnosed in all women with subcompensated placental insufficiency. In all cases, the first degree of severity of fetal growth retardation syndrome (FGR) of the asymmetric type was identified. Most often, FGR was noted in the main group (14%, vs 6.6% in the second group). Studies of progesterone levels showed a smooth, constant increase in progesterone in all groups, but in groups with hyperprolactinemia the values were shifted to the lower limit of the normative level, which was statistically significant when compared with the control group ( $p<0.05$ ). We believe that the true levels of progesterone in the first trimester are significantly lower than those determined due to tests performed against the background of gestagen correction. Analysis of TBG indicators did not reveal significant differences in the first and second trimesters; at 26-28 weeks, a statistically significant excess of TBG indicators was noted in the comparison group  $137.02\pm14.2$  mg/l relative to the control group  $100.12\pm11.2$  mg/l ( $p<0.05$ ), which can be regarded as a "strain" of placental function. The level of estriol in the groups with hyperprolactinemia did not go beyond the acceptable values, but from 22-24 weeks the increase in indicators was less than in the control group. By 37 weeks, estriol levels in pregnant women with hyperprolactinemia were significantly lower than those in the control group and amounted to  $4.89\pm0.56$  ng/ml in the main group,  $5.34\pm0.59$  ng/ml in the comparison group, and  $8.31\pm0.73$  ng/ml ( $p<0.05$ ).

A feature of childbirth in women with hyperprolactinemia was the high frequency of surgical delivery - in 80% of cases in the main group (of which 30% - according to the testimony of a neurosurgeon) and in 40% in the comparison group; high frequency of labor anomalies - in 60.7% and 42.4% of cases, respectively. The development of hypotonic bleeding in the subgroup with concomitant endocrine pathology was noted in 15% of cases compared to 3.3% of cases in the subgroup without concomitant endocrine pathology. The postpartum period in the group with combined endocrine pathology was complicated by the development of hematometra in 15% of cases, endometritis in 5% of cases.

## 6. Conclusions

The most characteristic complication of the gestation process with this endocrinopathy should be considered early pregnancy loss (16.1%). Spontaneous termination of pregnancy in such patients occurs against the background of relatively low levels of protein and steroid hormones of the trophoblast, which is confirmed by pathological examination data.

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