ScienceAsia
A peer-reviewed journal jointly published by
THE SCIENCE SOCIETY OF THAILAND
AND THE NATIONAL RESEARCH COUNCIL OF THAILAND
Online access : http://www.scienceasia.org

Volume 48 Number 3
June 2022
ISSN 1513-1874 CODEN : SCIASFZ
48(3):247-378 (2022)

ScienceAsia

Morphological changes of fungal-infected silkworms

RESEARCH ARTICLE
doi: 10.2306/ scienceasia1505-1516.2022.SE014

ScienceAsia 48 (2022): ***69-75***

Management of women with prolactinomas during pregnancy

Kh.K. Nasirova[a*], Yu. M. Urmanova[b], F.S. Khodzhaeva[c], U.Z. Mirzayeva[c], D.T.Mukhammedaminova[c]

[a] Associate professor, TashPMI Department of Endocrinology, Tashkent, Uzbekistan
[b] Professor, TashPMI Department of Endocrinology, Tashkent, Uzbekistan
[c] Assistant, TashPMI Department of Endocrinology, Tashkent, Uzbekistan

*Corresponding author, e-mail: hursh77@mail.ru

Received 7 Jan 2021
Accepted 28 Apr 2022

ABSTRACT: Prolactinomas are the most prevalent functional benign pituitary tumors due to a pituitary micro- or macroadenoma. The majority of patients presents with infertility and gonadal dysfunction. A dopamine agonist (DA) (bromocriptine or cabergoline) is the treatment of choice that can normalize prolactin levels, reduce tumor size, and restore ovulation and fertility. Cabergoline generally preferred over bromocriptine because of its higher efficacy and tolerability. Managing prolactinomas during pregnancy may be challenging. During pregnancy, the pituitary gland undergoes global hyperplasia due to a progressive increase in serum estrogens level that may lead to increase of the tumor volume with potential mass effect and visual loss. The risk of tumor enlargement may occur in 3% of those with microadenomas, 32% in those with macroadenomas that were not previously operated on, and 4.8% of those with macroadenomas with prior ablative treatment. Though both drugs appear to be safe during pregnancy, the data on fetal exposure to DAs during pregnancy have been reported with bromocriptine far exceeds that of cabergoline with no association of increased risk of pregnancy loss and premature delivery. It is advisable to stop the use of DAs immediately once pregnancy is confirmed, except in the case of women with invasive macroprolactinomas or pressure symptoms. This review outlines the therapeutic approach to prolactinoma during pregnancy, with emphasis on the safety of available DA therapy.

KEYWORDS: prolactin, pituitary tumor, dopamine agonist, pregnancy and outcome.

INTRODUCTION

Many studies have already been carried out in the world and there are data on the course of pregnancy and childbirth in women while taking dopamine agonists [1,4]. We conducted a prospective analysis of the course and outcomes of pregnancies that occurred after infertility treatment in 114 patients with prolactinomas.

Features of the course of pregnancy and childbirth in patients with prolactinomas are quite controversial. Most often, the authors of publications devoted to this problem emphasize the prevalence of such pregnancy complications as miscarriage. Most miscarriages occur in the first trimester of pregnancy; spontaneous abortion occurs much less frequently in the second trimester [2,3]. In our study, every third patient with microprolactinoma (30.7%) and two out of three patients with macroprolactinoma noted the threat of miscarriage (Table 1) (p_1<0.01, p_2<0.005, p_3<0.001). Toxicosis of the first half of pregnancy was observed in 58.9% of patients with microprolactinoma and in 80.9% of patients with macroprolactinoma (p_1<0.05), which is 1.5 and 2 times higher than the values of the control group (40%), p_2<0.05. Pathology of the number of amniotic water (oligohydramnios and polyhydramnios) differed slightly from the control group, which is explained by the presence or absence of an infectious agent as an etiological factor, and not by the pathology of the endocrine system. One of the terrible complications of the III

trimester was the development of preeclampsia 3.8 and 4.7% with prolactinoma; did not occur in the control group. Fetoplacental insufficiency (FPI) was more than 2 times more common in macroprolactinoma (19.04%) than in microprolactinoma (8.9%). Edema of pregnant women with macroprolactinoma occurred in almost every second patient (47.6%), with microprolactinoma in 42.3% of cases.

Table 1
Course of pregnancy in women with prolactinomas, %/abs

Complications	Microadenoma, n=78	Macroadenoma, n=21	Control group, n=20	p
Miscarriage	30.7/24	61.9/13	10/2	$p_1<0.01$ $p_2<0.005$ $p_3<0.001$
Toxicosis of the first half of pregnancy	58.9/46	80.9/17	40/8	$p_1<0.05$ $p_2<0.005$ $p_3<0.001$
Polyhydramnios	10.2/8	19.04/4	15/3	$p_1\geq0.3$ $p_2\geq0.7$ $p_3\geq0.5$
Oligohydramnios	5.1/4	-/0	5/1	$p_1\geq0.6$ $p_2\geq1.0$ $p_3\geq1.0$
Preeclampsia	3.8/3	4.7/1	-/0	$p_1\geq0.3$ $p_2<0.01$ $p_3<0.01$
Fetoplacental insufficiency	8.9/7	19.04/4	5/1	$p_1\geq0.2$ $p_2\geq0.5$ $p_3\geq0.17$
Edema	42.3/33	47.6/10	10/2	$p_1<0.05$ $p_2\geq0.08$ $p_3<0.05$

Note: statistical significance is presented: p_1 - between macro- and microprolactinomas, p_2 - between macroprolactinoma and control values, p_3 - between microprolactinoma and control values.

MATERIALS AND METHODS

Pregnancy outcome analysis showed that spontaneous abortions occurred in 15.3%, abortion for medical reasons in 2.6% and non-developing pregnancy in 2.6% of women with microprolactinoma, preterm birth in 11.5%, which in total amounted to 32% of cases of pregnancy loss (Table 2). With macroprolactinoma, these figures were as follows - spontaneous miscarriage - 19.4%, premature birth - 9.5%, non-developing pregnancy and interruption for medical reasons in this subgroup, we did not observe, the amount of pregnancy loss was - 28.9%. In most women, the cessation of fetal development occurred at the 6-7th week of pregnancy. In patients with prolactinomas with an interrupted pregnancy for a period of 6 weeks, a statistically significant decrease in the average concentrations of progesterone and activin in the blood serum was found. On average, the level of PRL in patients with miscarriage slightly exceeded the levels of the hormone in women with advanced pregnancy, however, no statistically significant difference was found. Many authors consider hypothyroidism, uterine hypoplasia, and disease duration over six years as risk factors for reproductive losses in this pathology [5].

Table 2.
Pregnancy outcomes in women with prolactinomas, %/abs

Complications	Microadenoma, n=78	Macroadenoma, n=21	Control group, n=20	p
Spontaneous miscarriage	15.3/12	19.4/4	-/0	$p_1\geq0.6$ $p_2\geq0.62$ $p_3\leq0.04$
Non-developing pregnancy	2.6/2	-/0	-/0	$p_1\geq1.0$ $p_2\geq0.47$ $p_3\leq0.04$
Preterm birth	11.5/9	9.5/2	5/1	$p_1\geq0.8$ $p_2\geq0.6$ $p_3\leq0.57$
Termination of pregnancy for medical reasons	2.6/2	-/0	-/0	$p_1\geq0.46$ $p_2\geq0.47$ $p_3\leq1.0$
Urgent birth through natural birth canal	48.7/38	42.8/9	80/16	$p_1\geq0.63$ $p_2<0.01$ $p_3\leq0,01$
Weak labor activity	7,6/6	19,04/4	10/2	$p_1\geq0.12$ $p_2\geq0,74$ $p_3\geq0,4$
Fetal hypoxia	32/25	42,8/9	10/2	$p_1\geq0.2$ $p_2\geq0,56$ $p_3\geq0,1$
Caesarian section	20,5/16	28,6/6	15/3	$p_1\geq0.3$ $p_2\geq0,57$ $p_3\geq0,3$
Untimely rupture of amniotic fluid	12,8/10	38,1/8	10/2	$p_1<0.01$ $p_2\geq0,7$ $p_3<0,05$
Bleeding in the postpartum period	5,1/4	14,3/3	-/0	$P_1\geq0.08$ $p_2\geq0,3$ $p_3\leq0,04$

Note: statistical significance is presented: p_1 - between macro- and microprolactinomas, p_2 - between macroprolactinoma and control values, p_3 - between microprolactinoma and control values.

In our study, urgent delivery through the natural birth canal was 48.7% with microprolactinoma and 42.8% with macroprolactinoma. According to our observations, 12.8% with microprolactinomas had untimely rupture of amniotic fluid, and with macroprolactinomas, this figure was almost 3 times higher, amounting to 38.1% (p_3<0.05). The presence of a mass effect of prolactinoma may be an aggravating factor in labor activity. The same trend was observed in terms of the weakness of labor activity - 7.6% for microprolactinoma and 19.04% for macroprolactinoma. In our studied patients with prolactinomas, there were complications of labor activity in microprolactinoma - premature rupture of amniotic fluid (12.8%), weakness of labor activity (7.6%), fetoplacental insufficiency (32%) - were higher than in the same age group of healthy pregnant women, and with macroprolactinoma, these figures were higher - 38.1%: 19.04%: 42.8%. The percentage of operative delivery in prolactinomas (on average in 25% of the observation) was higher than in the control group (15%).

All of our patients were breastfed until the end of the neonatal period, then, due to a decrease and / or lack of lactation, they switched to a mixed diet - 17.4% (n=11) of patients from the microprolactinoma group and 16.6% (n=3) of group of macroprolactinomas.

If analyze using the Apgar scale, we obtained significant differences in the micro- and macroprolactinoma group with the data of the control group at 1 minute after birth (Table 3), p_2<0.03, p_3<0.02.

Considering the increased frequency of spontaneous abortions and low progesterone levels (Table 3), we prescribed progestogen replacement therapy (dydrogesterone) to all patients from the moment of diagnosis of pregnancy to the 16-week period. The presence of subclinical hypothyroidism in 19.2% of patients with microprolactinoma and in 23.8% of patients with macroprolactinoma dictated the need to prescribe euthyrox (levothyroxine sodium) in individual doses (Fig. 1). Given the above data, our patients during pregnancy took cabergoline to suppress prolactin secretion - 71.4% of patients with microprolactinoma and 43.5% with macroprolactinoma.

Table 3

Assessment of the condition of the fetus in pregnant women with prolactinomas

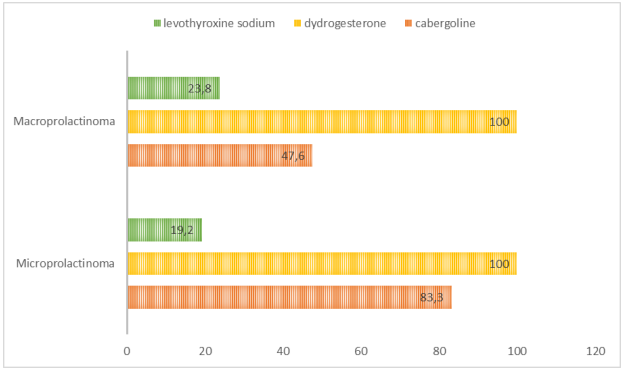
Indicator	Microadenoma, n=78	Macroadenoma, n=21	Control group, n=20	p
Height, cm	51,5±1,3	51,8±1,6	51,8±1,6	p_1≥0,2 p_2≥0,2 p_3≥0,9
Weight o fetus, g.	3367,1±328,3	3426±470	3424±492	p_1≥0,5 p_2≥0,6 p_3≥0,4
Apgar scale, points				
1 min.	7,5±0,55	6,45±0,51	7,8±0,53	p_1≥0,5 p_2<0,03 p_3<0,02
5 min.	8,3±0,66	7,4±0,6	8,6±0,5	p_1≥0,4 p_2≥0,07 p_3≥0,06

Note: statistical significance is presented: p_1 - between macro- and microprolactinomas, p_2 - between macroprolactinoma and control values, p_3 - between microprolactinoma and control values.

RESULTS AND DISCUSSION

Figure 1.

Therapy during pregnancy, %

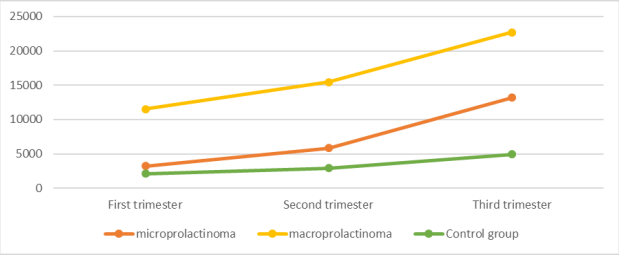


According to MRI of the chiasmal-sellar area, performed during the first two months after delivery, there was no progression of growth of pituitary adenomas.

Analysis of PRL secretion during pregnancy showed the following. With the increase in the duration of pregnancy, the secretion of PRL increased, reaching a maximum in the third trimester (Fig. 2). But in comparison by subgroups, we received significantly high numbers in the subgroup with

macroprolactinoma, so with macroprolactinoma in the first trimester, the PRL level was 11541±1871 ng/ml compared with the microprolactinoma subgroup - 3200±678 ng/ml (p_1<0.0001) against the values control group - 2105±632 ng/ml (p_2<0.0001, p_3<0.0001). In the second trimester, these figures corresponded to -15450±1563 ng/ml in macroprolactinoma (p_3<0.0001), 5850±1338ng/ml in microprolactinoma (p_2<0.0001), 2940±1012 ng/ml in the control group. In the III trimester, the figures were the highest - 13200±3685 ng/ml with microprolactinoma (p_2<0.0001), 22677±1516 ng/ml with macroprolactinoma (p_3<0.0001), and in the control group - 4945±1431 ng/ml .

Figure 2.
Dynamics of prolactin levels during pregnancy in patients with prolactinomas, ng/ml.



If analyze in comparison with the control, then with microprolactinoma, the level of prolactin was 1.5 times higher in the first trimester, 1.9 times higher in the second trimester and 2.6 times higher in the third trimester; with macroprolactinoma - 5.4: 5.2: 4.6 times higher compared with the control in trimesters of pregnancy (reference values correspond to 0-2000 ng / ml in the first trimester, 0-6000 ng / ml in the II trimester, in the III trimester - 0-10000 ng / ml).

Table 4
Data from hormonal examination during pregnancy in women with prolactinomas

Indicator	Microadenoma, n=78	Macroadenoma, n=21	Control group, n=20	p
I trimester				
Prolactin, ng/ml	3200±678	11541±1871	2105±632	p_1<0,0001 p_2<0,0001 p_3<0,0001
TSH, mIU/l	3,1±0,5	3,2±0,5	2,6±0,8	p_1≥0,53 p_2<0,001 p_3<0,001
FT4, ng/dl	1,4±0,26	1,4±0,3	1,5±0,3	p_1=0,67 p_2≥0,3 p_3=0,21
TPO Ab, IU/ml	10,56±1,2	14,1±1,8	15,7±1,1	p_1≥0,4 p_2≥0,5 p_3≥0,6
Progesterone, nmol/l	10,48±3,8	7,9±3,2	143±17,3	p_1=0,005 p_2<0,0001 p_3<0,0001
Estradiol, pg/ml	42,5±11,8	40,8±5,3	435,8±171,3	p_1=0,5 p_2<0,0001 p_3<0,0001
II trimester				
Prolactin, ng/ml	5850±1338	15450±1563	2940±1012	p_1<0,0001 p_2<0,0001 p_3<0,0001
TSH, mIU/l	3,3±0,67	3,5±0,7	2,9±0,7	p_1≥0,3 p_2<0,001 p_3<,001
FT4, ng/dl	1,5±0,26	1,5±0,32	1,6±0,1	p_1=0,7 p_2=0,29 p_3=0,17
TPO Ab, IU/ml	13,5±2,1	13,8±2,7	13,5±1,9	p_1≥0,8 p_2≥0,62 p_3≥0,6
Progesterone, nmol/l	71,2±8,4	67,8±7,2	187±59	p_1=0,09 p_2<0,0001 p_3<0,0001
Estradiol, pg/ml	665,3±70,8	625,7±95,7	5189±2502	p_1<0,05 p_2<0,0001 p_3<0,0001
III trimester				
Prolactin, ng/ml	13200±3685	22677±1516	4945±1431	p_1<0,0001 p_2<0,0001 p_3<0,0001
TSH, mIU/l	3,1±0,3	3,3±0,5	3,1±0,6	p_1≥0,26 p_2<0,001 p_3<0,001
FT4, ng/dl	1,4±0,7	1,5±0,09	1,5±0,8	p_1=0,7 p_2=0,29 p_3-0,17
TPO Ab, IU/ml	13,6±14,98	13,2±1,7	14,5±0,7	p_1≥0,8 p_2≥0,7 p_3≥0,6
Progesterone, nmol/l	98,85±11,75	95,2±11	370±105,8	p_1=0,2 p_2<0,0001 p_3<0,0001
Estradiol, pg/ml	555±19,0	510±5,2	5611±2325	p_1≥0,3 p_2<0,0001 p_3<0,0001

Note: statistical significance is presented: p_1 - between macro- and microprolactinomas, p_2 - between macroprolactinoma and control values, p_3 - between microprolactinoma and control values.

Thyroid status did not undergo significant fluctuations in trimesters of pregnancy in comparison with control values. But since the target values for TSH during pregnancy are up to 2.5 mIU / l, 19.2% of patients from the microprolactinoma group took levothyroxine sodium according to an individually selected scheme, in the presence of an appropriate clinical picture, and 23.8% of patients from the group with macroprolactinoma.

The level of ovarian steroid hormones responsible for the normal prolongation of pregnancy and childbirth were depressed throughout pregnancy, possibly due to hyperprolactinemia (table 4). So the level of progesterone was more than 10 times lower than the control values in patients in the first trimester of pregnancy, and more pronounced in macroprolactinoma, which dictated the appointment of dydrogesterone to all patients

with prolactinomas up to 16 weeks of pregnancy (p_2<0.0001, p_3<0.0001). In the second trimester of pregnancy, this indicator had a positive trend, but did not reach the control values: with microprolactinoma, the level of PRL was 2.6 times lower than the control, with macroprolactinoma - 2.7 times (p_2<0.0001, p_3<0.0001) . In the III trimester - 3.7 times lower than the control with microprolactinoma and 3.8 times with macroprolactinoma. II trimester - 7.8 times lower, in the III trimester - 10 times lower; with macroprolactinoma in the 1st trimester - 10.6 times lower, in the 2nd trimester - 8.3 times, in the 3rd trimester - 11 times (p_2<0.0001, p_3<0.0001). The importance of estrogens in pregnancy is obvious, but their role seems to be inferior to that of progesterone. During pregnancy, estrogens stimulate LDL uptake by syncytiotrophoblasts, promoting steroid production, increase uterine blood flow, which ensures adequate gas exchange and transport of nutrients across the placenta, and induce hypertrophy of breast tissue, preparing them for feeding [10]. In the III trimester there is a high incidence of edema (25%), premature birth (11.1%), placental insufficiency. According to the ultrasound of the uterus, 47% of patients with prolactinoma showed signs of premature maturation of the placenta, hemodynamic disturbances in the aorta and middle cerebral artery of the fetus. Signs of chronic fetal hypoxia were identified according to cardiotocography in 34.3% of cases.

As described above, the main source of inhibins during pregnancy is the fetoplacental complex. At the same time, from early pregnancy, the level of inhibin A gradually increases. In this regard, the level of inhibin A is used as an important and promising marker for diagnosing pregnancy complications [6,11]. According to our observations, the level of inhibin A during pregnancy in patients with prolactinomas was higher than in the control group. Thus, in the first trimester in patients with microprolactinomas, its level was 23.5±2.4 ng/ml (p_2 <0.001) , with macroprolactinoma 25.02±1.8 ng/ml (p_3<0.001), in the control group - 22±1.4 ng/ml. In the II trimester, these figures were 32±3.6 ng/ml (p_2<0.001), 36.7±1.8 ng/ml (p_3<0.001) compared to 31.3±2.1 ng/ml (table five).

Table 5

TGF during pregnancy in women with prolactinomas

Indicator	Microadenoma, n=78	Macroadenoma, n=21	Control group, n=20	p
I trimester				
Inhibin A, ng/ml	23,5±2,4	25,02±1,8	22±1,4	p_1≥0,4 p_2 <0,001 p_3<0,001
Inhibin B, pg/ml	61,9±10,4	60,24±10,3	61,7±1,05	p_1=0,5 p_2≥0,9 p_3=0,5
Activin, pg/ml	7,4±2,7	7,8±2,5	5,1±0,4	p_1≥0,6 p_2<0,01 p_3<0,01
AMH, ng/ml	2,71±1,03	2,44±0,84	3,2±0,12	p_1=0,4 p_2<0,01 p_3<0,001
II trimester				
Inhibin A, ng/ml	32±3,6	36,7±1,8	31,3±2,1	p_1=0,4 p_2<0,001 p_3<0,001
Inhibin B, pg/ml	61,7±9,2	61,3±10,7	62,1±1,8	p_1 ≥0,8 p_2=0,4 p_3=0,6
Activin, pg/ml	5,8±2,1	5,7±2,2	4,9±0,3	p_1≥0,9 p_2≥0,17 p_3=0,28
AMH, ng/ml	2,68±0,9	2,77±0,7	3,11±0,09	p_1=0,6 p_2<0,01 p_3<0,05
III trimester				
Inhibin A, ng/ml	47,7±2,8	50,7±2,3	42±1,9	p_1=0,4 p_2<0,001 p_3<0,001
Inhibin B, pg/ml	64,2±4,4	63,6±5,2	62,2±1,6	p_1≥0,6 p_2≥0,8 p_3≥0,4
Activin, pg/ml	4,1±2,5	4,09±2,8	4,45±0,2	p_1=0,87 p_2≥0,12 p_3≥0,15
AMH, ng/ml	2,63±0,9	2,29±0,75	3,17±0,08	p_1≥0,12 p_2<0,005 p_3<0,001

Note: statistical significance is presented: p_1 - between macro- and microprolactinomas, p_2 - between macroprolactinoma and control values, p_3 - between microprolactinoma and control values.

In the III trimester, respectively - 47.7±2.8 ng/ml with microprolactinoma (p_2<0.001), 50.7±2.3 ng/ml with macroprolactinoma (p_3<0.001), in healthy pregnant women - 42±1.9 ng/ml.

The results of numerous studies have shown that in pregnant women with preeclampsia and placental insufficiency there is a sharp increase in the level of inhibin A, which made it possible to use the determination of the level of inhibin A to diagnose these complications of pregnancy [191; from. 109-112]. We analyzed data from patients with prolactinoma who had preeclampsia and postpartum hemorrhage and performed a Pearson correlation analysis that showed a marked negative correlation between estradiol and inhibin A (r=-0.601), (p<0.0001). That gave us the basis for calcula-

ting the ratio of the level of estradiol to inhibin A to predict the risk of developing the pathology of the third trimester in patients with prolactinomas (table 6). As a result, we found that with the ratio of estradiol to inhibin A<2 in the first trimester of pregnancy in the presence of prolactinoma, the patient has an increased risk of preeclampsia and complications in the postpartum period.

Table 6
Correlation analysis and / coefficients for predicting the pathology of pregnancy (analysis of predictors of pregnancy complications)

Indicator	Microprolactinoma, n=78	Macroprolactinoma, n=12	p
Pathology of the first half of pregnancy (threatened miscarriage, spontaneous miscarriage, non-developing pregnancy)			
Progesterone/Activin	1,4 r= (-)0.81	1,0 r= (-)0.9	<0,0001
Pathology of the second half of pregnancy and childbirth (preeclampsia, bleeding in the postpartum period)			
Estradiol/inhibin A	< 2 r= (-)0,673	< 2 r= (-)0,601	<0,0001

The level of inhibin B during pregnancy practically did not differ from the values of the control group: in the first trimester, no significant differences were found: with microprolactinoma - 61.9±10.4 pg/ml, with macroprolactinoma - 60.24±10.3 pg/ml , in healthy pregnant women - 61.7±1.05 pg/ml. In the II trimester, a significant increase was observed compared with the control group: with microprolactinoma, the level was 61.7 ± 9.2 pg / ml, with macroprolactinoma 61.3 ± 10.7 pg / ml, in the control group - 62.1 ± 1, 8 pg / ml. In the III trimester, the level of inhibin B was below the control values (p<0.0001).

Analysis of activin secretion during pregnancy in patients with prolactinomas showed the following: in the first trimester with microprolactinoma it was 7.4±2.7 pg/ml, with macroprolactinoma it was 7.8±2.5 pg/ml, which is significantly higher than the control values (p_2<0.01, p_3<0.01). Moreover, the maximum numbers were observed in patients with miscarriage. In the II and III trimesters, significant fluctuations in the level of activin were not detected - with microprolactinoma 5.8±2.1 pg/ml in the 2nd trimester, 4.1±2.5 pg/ml in the third trimester, with macroprolactinoma - 4.1±2 .5 pg / ml and 4.09 ± 2.8 pg / ml, respectively, in comparison with the control - 5.1 ± 0.4 pg / ml. It is known that activin inhibits the growth of vascular endothelium, together with TGFβ can inhibit capillary growth during trophoblast invasion, which is exacerbated by the relative lack of progesterone [8,9]. Given the relative deficiency of progesterone in prolactinomas, we were interested in linking these two indicators - the ratio of progesterone to activin in the first trimester of pregnancy to predict pregnancy losses in the early stages. Since the correlation analysis according to the Pearson method showed that there is a strong negative relationship between activin and progesterone (r = -0.81), (p<0.0001), and the indicators were statistically significant (in the microprolactin group). The calculation showed that with the ratio of progesterone to activin <1.4 in the first trimester of pregnancy in the presence of microprolactinoma and <1.0 in macroprolactinoma in the patient increases the risk of spontaneous miscarriage, non-developing pregnancy. Thus, even before the start of treatment, an unfavorable outcome of pregnancy can be assumed. Nevertheless, the refusal of preservation therapy on the basis of the belief that already at the initial stages of implantation there are profound changes leading to miscarriage, can be considered euthanasia for the embryo, which is certainly unacceptable.

An analysis of the content of AMH in the blood serum showed that in patients whose pregnancy proceeded against the background of prolactinoma, there were no significant fluctuations.

CONCLUSION

Thus, patients with prolactinomas during pregnancy are characterized by the threat of miscarriage (30-55%), toxicosis of the first half of pregnancy was observed in 58.9% of patients with microprolactinoma and in 80.9% of patients with macroprolactinoma, untimely discharge of amniotic fluid with macroprolactinomas, it was observed almost 3 times more often than with microprolactinomas. Also revealed suppression of the secretion of transforming growth factors - inhibin A, B, activin. Despite the ongoing

therapy, hyperprolactinemia was observed throughout pregnancy, which naturally led to relative hypoestrogenemia and hypoprogesteronemia with leading symptoms of miscarriage, fetal hypoxia. A negative relationship was found between progesterone and activin, which is a predictor of the pathology of the first trimester, as well as estradiol and inhibin A, which may indicate pathology of the third trimester and the postpartum period. These diagnostic and prognostic coefficients will help predict the risks and outcomes of pregnancy.

REFERENCES

1. Bykanova N.S., Pigarova E.A. Hyperprolactinemia and pregnancy: main achievements and unresolved issues /N.S. Bykanova, E.A. Pigarova // Bulletin of Reproductive Health. -2011. – Vol. 1. – pp. 16-21.
2. Dzeranova L.K. et al. Pregnancy and hyperprolactinemia in the clinical practical recommendations of the International Endocrinological Society for the diagnosis and treatment of hyperprolactinemia/ L. K. Dzeranova, N. S. Bykanova, E. A. Pigarova // Bulletin of Reproductive Health. - 2011. – No. 2 (June). – pp. 42-44.
3. Korsak V.S. And others . Register of ART centers in Russia. Report for 2015 / V.S. Korsak, A.A. Smirnova, O.V. Shurygina // Problems of reproduction. -2017.- №23(5).- P.8–22.
4. Boyarsky K. Yu. The role of ovarian reserve indicators in the treatment of infertility by IVF-PE/K.Yu. Boyarsky // Treatment of female and male infertility (assisted reproductive technologies) / ed. V. And Kulakov., B. V. Leonov., L. N. Kuzmichev. — Moscow: MIA, 2005. — pp. 53-60.
5. Glezer A., Bronstein M.D. (2019) Prolactinomas during pregnancy: considerations before conception and during pregnancy // Pituitary gland.
6. Ding D., Stark R.M., Sheehan J.P. Paradigms of pituitary adenoma treatment: determining the role of radiosurgery and radiation therapy // J Neurooncol.- 2014.- №117(3).- Pp.445-457.
7. Kondi-Paphiti A., Grigoriadis S., Samiotaki D., etc. Immunohistochemical study of the expression of inhibins A and B in placentas during normal and pathological pregnancy // Clinical obstetric gynecology.- 2013.- №40(1).- Pp.109-112.
8. Vijayaratna R., de Kretser D.M. Activins in reproductive biology and beyond// Updating Hum Reprod. -2016.- № 22(3).- P.342-357.
9. Eding Andersen S. Inhibin-B secretion and distribution of FSH isoforms can play an integral role in follicular selection in the natural menstrual cycle // Mol Hum Reprod. -2017.-№23(1).- P.16-24.
10. Zada G., Woodmancy U.U., Ramkissun S., Amadio J., Nos. V., Lowes E.R. Jr. Atypical pituitary adenomas: frequency of occurrence, clinical characteristics and consequences // Neurosurgery. - 2011. – Vol.114, No. 2. – pp.336-344.,
11. Namvange M., Brown K.U. Activins and inhibins: role in development, physiology and diseases // Cold Spring Harb Perspective Biol.- 2016.- № 8(7).- Pp. 456-468.