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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

**PECULIARITIES OF PREGNANCY, CHILDBIRTH IN LATE
REPRODUCTIVE AGED WOMEN, MODERN METHODS OF
CORRECTION OF CHRONIC PLACENTA**

Speciality: 3215.01 – Obstetrics and gynecology

Field of science: Medicine

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Baku – 2022

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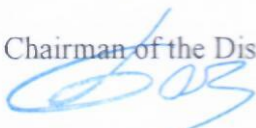
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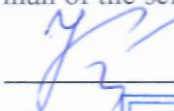
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GENERAL CHARACTERISTICS OF WORK

Relevance of the topic. In recent years, the principles of dispensary observation of pregnancies and optimal delivery of women of late reproductive age (35 and older) have attracted attention as an urgent problem. The increase in the number of pregnant women of late reproductive age in this general population is due to complications that may occur during pregnancy, childbirth and postpartum. Many scientists consider the age of a woman as an independent risk factor among the factors that determine the course of hestasis, and characterize such a pregnancy as a "problematic" pregnancy in advance^{1,2,3}

In many countries of the world, including our republic, the number of women giving birth for the first and second time of late reproductive age is growing. This is primarily due to the growing role of women in society, their late marriages, years of infertility treatment, financial difficulties to use assisted technology, previous pregnancy losses, recurrent miscarriages and perinatal deaths^{4,5}.

There is no consensus in the literature on safe pregnancies and births in women of late reproductive age. According to many researchers, late reproductive age increases the risk of chronic malnutrition, somatic, genital diseases, incomplete pregnancies

¹Аюбова, Т.К. Возраст женщины как медико-социальный фактор риска по материнской и перинатальной патологии и разработка организационных подходов по его устранению // – Москва: Социальные аспекты здоровья населения, – 2015. №5(45), – с. 1-7.

²Кравченко, М.А., Смирнова Т.И. Первородящие старше 35 лет: течение беременности, родов, состояние новорожденных // – Смоленск: Смоленский медицинский альманах, – 2016. №4, – с. 158-161.

³Ситникова, Л.Н., Лавлинская, Л.И. Организация медицинской помощи беременным групп высокого риска // – Тула: Вестник новых медицинских технологий. Электронное издание, – 2014. №1.

⁴Горюнова, А.Г. Синдром задержки роста плода и адаптации плаценты / А.Г.Горюнова, М.С.Симонова, А.В.Мурашко // Архив акушерства и гинекологии им. В.Ф. Снегирева, – Москва: –2016. Т. 3, №2, – с. 76-80.

⁵Игнатко, И.В. Прогностические маркеры синдрома задержки роста плода / И.В.Игнатко, М.М.Мирющенко // Медико-фармацевтический журнал «Пульс», – Калининград: – 2016. Т.18, №1, – с. 1-4.

(spontaneous miscarriage and premature birth), hypertensive conditions during pregnancy, birth defects, abdominal births, premature rupture of membrane, intrauterine growth retardation, hypoxia.. At the same time, perinatal mortality, perinatal morbidity, increase the frequency of maternal deaths. Therefore, women of late reproductive age are rightly included in the "risk group". In the absence of concomitant diseases, the course of pregnancy, childbirth and menopause in women of late reproductive age may be relatively good for both mother and fetus^{6,7}.

Due to complications of pregnancy and childbirth in women of late reproductive age, the number of abdominal births is many times higher than natural births. This, in turn, leads to bleeding, obstetric embolism, thromboembolism, purulent-septic diseases of the postpartum period, and, finally, maternal death due to these complications. On the other hand, pregnant women in this group (40-75% of all pregnancies) develop placental insufficiency⁸.

One of the possible ways to solve this problem is the use of ozone therapy called "medical ozone"⁹

Ozone therapy is a highly effective and cost-effective method that has a wide range of effects on the human body, which is achieved through the following therapeutic effects: bactericidal, fungicidal, virolytic, immunomodulatory, anti-hypoxic, stimulating

⁶*Кравченко, М.А., Смирнова, Т.И.* Первородящие старше 35 лет: течение беременности, родов, состояние новорожденных // – Смоленск: Смоленский медицинский альманах, – 2016. №4, – с. 158-161.

⁷*Ларюшева, Т.М.* Сравнительный анализ результатов доплерометрического исследования кровотоков в системе «мать-плацента-плод» и исходов родов у несоровершеннолетних женщин и женщин оптимального репродуктивного возраста / Т.М. Ларюшева, Н.Г. Истомина, А.Н. Баранов [и др.] // – Москва: Репродуктивное здоровье детей и подростков, – 2016. №3, – с. 74-79.

⁸*Деменина, Н.К.* Особенности беременности и родов у женщин старшего возраста (Обзор литературы) / Н.К.Деменина, Вл.В.Подольский, А.В.Сорокин [и др.] // Збірник наукових праць Асоціації акушерів-гінекологів України, – 2014. №1-2, – с. 107-109.

⁹*Андрющенко, В.В.* Актуальные вопросы практического применения парентеральной озонотерапии в медицине неотложных состояний / В.В.Андрющенко, Н.В.Курдиль, В.Ф.Струк [и др.] // Медицина неотложных состояний, – Киев: – 2019. №8(103), – с. 121-127.

regeneration, metabolism and increasing the body's antioxidant defenses¹⁰.

There are many scientific studies in the domestic and foreign literature on the application of ozone therapy in pregnant women with various pathological conditions^{11,12}. However, as is well known, the goal of any treatment during pregnancy is not only to reduce the frequency of pathology, but also to prevent possible complications for the fetus and newborn, as well as to protect it from the side effects of this type of treatment. In this regard, the study of the complications of ozone therapy during pregnancy for newborns and babies, especially in the first year of life, is of great practical interest.

Thus, the prediction of Chronic Placental Deficiency (CPI) on the basis of modern medical technologies for the purpose of correction, the search for pre-clinical diagnostic methods is an urgent problem.

Object of the research. Women of late reproductive age.

The purpose of the research was to improve the principles of rational management of women of late reproductive age, taking into account the characteristics of the gestation period and the course of childbirth in modern conditions.

Research objectives:

1. To study the characteristics of somatic and gynecological pathologies in women of late reproductive age;
2. To determine the structure of complications of pregnancy, childbirth and postpartum on the basis of clinical anamnesis in women of late reproductive age;
3. To assess the therapeutic effect of ozone therapy on the basis

¹⁰*Luongo, M.* Possible Therapeutic Effects of Ozone Mixture on Hypoxia in Tumor Development / M. Luongo, A.L. Brigida, L. Mascolo [et al.] // *Anticancer Res.* – 2017. 37, № 2, – p. 425-435.

¹¹*Bilge, A.* Could Ozone Treatment Be a Promising Alternative for Osteomyelitis? An Experimental Study / A. Bilge, Ö. Öztürk, Y. Adali [et al.] // *ActaOrtop. Bras.* – 2018. Vol. 26, №1, – p. 67-71.

¹²*Peirone, C.* Ozone Therapy Prevents the Onset of Dysplasia in HPV16-Transgenic Mice – A Pre-Clinical Efficacy and Safety Analysis / C. Peirone, V.F. Mestre, B. Medeiros-Fonseca [et al.] // *Biomed. Pharmacother.* – 2018. Vol. 104, – p. 275-279.

of studying the dynamics of clinical, hormonal, biochemical parameters under the influence of different types of treatment of pregnant women of late reproductive age.

4. To compare the condition of the fetoplacental complex in pregnant women of late reproductive age, depending on the treatment with medical ozone.

5. To study the effects of ozone therapy on the condition of the fetus and newborn in mothers of late reproductive age.

Research methods. Clinical-anamnestic, laboratory and instrumental research methods.

The main provisions of the dissertation for the defense:

- Women of late reproductive age have a high frequency of hestation and birth complications due to a complex of factors that cause obstetric and gynecological complications, age characteristics of the body, high somatic and gynecological diseases.
- Disruption of the formation of the maternal-placenta-fetal circulatory system in the early stages of pregnancy leads to complications of gestation and possible adverse effects on the mother and fetus.
- Prognostic criteria for the development of fetoplacental insufficiency and adverse course of pregnancy and childbirth in women of late reproductive age are an increase in the pulsation index in the uterine arteries and a decrease in volumetric circulatory indices.
- The developed algorithm of individual complex examination of women of late reproductive age with the formation of a high risk group in the first trimester of pregnancy allows to improve the quality of observation of pregnant women in the dispensary, prolong pregnancy until optimal delivery and improve perinatal results.

Scientific novelty of the research. As a result of the research, medical characteristics of women of late reproductive age were given and the characteristics of the course of gestation were studied.

A comprehensive examination of pregnant women of late reproductive age was conducted, and on the basis of the obtained

data, a more optimal complex diagnosis and treatment scheme of fetoplacental insufficiency was developed.

Direct and indirect exographic signs of placental abnormalities were found in women of late reproductive age. The applied ultrasound method and dopplerography are highly informative not only in diagnosis, but also in monitoring the effectiveness of treatment.

A system of measures has been developed to form risk groups for the development of placental insufficiency, spontaneous abortions and premature births.

The proposed treatment of pregnant women has shown its high effectiveness in reducing the frequency of placental insufficiency in the process of hestation and the improvement of perinatal outcomes.

Practical significance of the research. In women of late reproductive age, the frequency and structure of extragenital and gynecological diseases, the characteristics of the course of pregnancies and births have been studied in detail, which allows them to be included in the group of high birth and perinatal risk.

Ultrasound examinations, including complex exographic and dopplerographic indicators of the formation of the pair in the first and second trimesters of pregnancy, have been developed, which allow to predict the course of maternal and fetal circulation in the first and second trimesters of gestation.

The effectiveness of the proposed complex measures to improve the quality of dispensary control of pregnant women of late reproductive age with placental insufficiency has been proven.

Approbation. The main provisions of the dissertation were reported and discussed at the "Otto reports" III All-Russian scientific-practical conference for obstetricians and gynecologists (St. Petersburg, 2021).

The work was approved at a meeting of the I and II Departments of Obstetrics and Gynecology of Azerbaijan Medical University (AMU) (12.02.2019, protocol No. 01), at the scientific seminar of the Dissertation Council ED 2.06 at AMU (30.06.2021, protocol No. 12).

Implementation of research results into practice. The results of

the study were included in the educational process of the I Department of Obstetrics and Gynecology of AMU, as well as in the clinical practice of the Educational and Surgical Clinic of AMU and Clinical Maternity Hospital named after Sh. Alaskarova.

The name of the organization where the dissertation has been accomplished. The work was carried out at the I Department of Obstetrics and Gynecology of AMU.

Publications on dissertation material: 10 scientific works on the topic of the dissertation (7 articles, 3 theses), including published near and far abroad.

Volume and structure of the dissertation: The dissertation is published on 159 pages (191007 symbols) and consists of introduction (6 pages), literature review (28 pages), research materials and methods (11 pages), 2 chapters of results of own research and their discussion (54 pages), conclusion (32 pages), results (2 pages), practical recommendations (1 pages) and references list (19 pages). The bibliography includes 150 sources. 14 of them are in Azerbaijani, 102 of them in Russian, and 39 of them in other foreign languages. The work is illustrated with 46 tables, 6 charts and 1 scheme.

RESEARCH MATERIALS AND METHODS

In accordance with the set purpose, 90 pregnant women aged 35-45 years were examined.

The groups are divided as follows. The main group (I) had 30 previous pregnancies with complications and complex treatment with ozone therapy, the comparison group (group II) had 30 pregnancies with complications and treatment with drugs, the control group (group III) had physiological pregnancies and no 30 women who did not receive treatment were included.

Clinical and laboratory examinations of all patients were conducted in accordance with the existing standards of obstetric examination of the Clinical Maternity Hospital named after Sh. Alaskarova (Maternity Hospital No. 5) in Baku. Randomization was performed according to age, social factors, concomitant

gynecological and extragenital diseases.

Before being included in the study, all patients were examined according to a specific scheme consisting of the following clinical and laboratory methods:

Collection of anamnestic data (nature of menstruation, number of pregnancies, miscarriages, births and abortions, features of their course, the presence of complications; information about heredity, previous illnesses, the presence of bad habits).

- Objective examination.
- Gynecological examination.
- Ultrasound examination of the uterus (to determine the viability of the embryo).
- Commonly accepted laboratory tests.
- Uterine smear from the cervical canal to determine the degree of bacteriological culture and purity.
- Hemostasiological examination of blood.

Prospective observation of the course and consequences of pregnancy of pregnant women belonging to all groups was conducted.

Evaluation of the fetoplacental complex in the dynamics of pregnancy was carried out: ultrasound fetometry at 24-25, 30-31 weeks of pregnancy, dopplerometry (if indicated), cardiotocography every week after 33 weeks.

In order to make the results of the evaluation of the effectiveness of the treatment method as complete as possible, In the control and main groups of pregnant women, a set of special methods was used, including anthropometric measurements, generally accepted external and internal obstetric examination of pregnant women, as well as a comprehensive assessment of the "maternal-placental-fetus" system: dopplerometry, fetal cardiotocography (CTG), USM of the fetus and placenta, fetometry, morphometry of the fetus and newborn, as well as laboratory control of a number of biochemical parameters that give an objective description of the condition of the fetus during pregnancy (table 1).

Table 1**Total volume of examination methods of observed pregnant women with Placental insufficiency**

№	Type of examination	Number of patients examined
1	Obstetric examination	410
2	Ultrasonography of fetus and placenta	360
3	Cardiography of the fetus	180
4	Biophysical profile of the fetus	90
5	Dopplerometry of the vessels of the placenta	180
6	Apgar score assessment	90
7	Coagulogram, biochemical analysis of blood	270
8	Anthropometric examination of newborns	90
9	Neonatal cranial ultrasonography	90

Methods of ozone therapy. The first course is conducted in main group for 5 days in the 10-12th weeks of pregnancy. It is injected by infusion of 200 ml of a solution containing 2 µg / ml of ozone. The second course is performed at 18-20 weeks of pregnancy. 250-300 ml of ozonated saline with a concentration of 2-3 mcg / ml of ozone is injected for 7-8 days. The third course is applied on the 28th and 32nd days of pregnancy. 250-300 ml of ozonated saline with a concentration of 2-3 mcg / ml of ozone is injected for 8-10 days.

Drug treatment of fetoplacental insufficiency in the comparison group was carried out according to the protocol adopted by the Ministry of Health of the Republic of Azerbaijan.

Statistical processing. During the statistical processing of the series of variations constructed for all parameters, the mean (M-Mean), the value of the standard deviation (σ = Std. Dev.) And the standard error (t = Std. Error) were calculated. The accuracy of the differences between the indicators was assessed using the Student's t-

criterion in the case of a normal distribution of the indicators. When comparing quantitative characteristics, the statistical difference between the independent samples was determined using the non-parametric Manna-Whitney U-criterion and the White T-criterion. Precise χ^2 and Fisher criteria were used to determine the statistical difference between the quality characteristics of the groups.

The difference between the indicators was considered statistically significant at least $p < 0.05$. The statistical significance of the differences was accepted on at least two criteria.

RESULTS OF RESEARCH AND ITS DISCUSSION

90 pregnant women aged 35-45 years were examined. The analysis of gynecological anamnesis showed that the age of onset of the first menstruation ranged from 9 to 16, it is organized with an average of 13.7 ± 1.1 . In 65.5% (59) of patients, the menstrual cycle was regular, with the duration of menstruation varying from 3 to 7 days. In the control group, the number of women whose menstrual cycle was not disrupted before the onset of pregnancy was significantly higher - 19 (63.3%).

Inflammatory diseases of the genitals predominated in the structure of gynecological diseases: erosion of the cervix was detected in 12 (40%) cases in the main group, 12 (40%) cases in the comparison group, and 4 (13.3%) cases in the control group. Chronic endocervicitis was detected in 10 (33.3%) patients in the main group, 11 (36.7%) patients in the comparison group, and 4 (13.3%) patients in the control group. Chronic salpingo-oophoritis was detected in 15 (50%) cases in the main group, 16 (53.3%) cases in the comparison group, and 5 (16.7%) cases in the control group.

During the study of obstetric history, it was found that 18 (60%) pregnant women in the main group, 14 (46.6%) pregnant women in the comparison group, and 19 (63.3%) women in the control group gave childbirth delivery again. 29 (96.6%) women had a history of medical abortions, in the main group, 30 (100%) women in the comparison group, 11 (36.6%) women in the control group. The emergence of an inflammatory process as a complication in pregnant

women of the comparison group during artificial abortion occurred twice as often as in the main group and bleeding occurred in 13 patients. In the main group of women, in many cases, previous pregnancies ended in spontaneous miscarriages - 9 (30%), in the comparison group, such women were 9 (30%). In all of the women examined, the current pregnancy was a repeat pregnancy.

Given the high specific gravity of the failures of the previous gestation, an attempt was made to determine the nature of the course of previous pregnancies by us - each of the 30 women with a history of pregnancy in the main group was hospitalized due to the risk of early miscarriage. Pregnancy in 7 (23.3%) women was terminated at 22-24 weeks of gestation according to medical indications, in the main group, the pregnancies of 3 (10%) pregnant women were extended to the physiological time of delivery and and childbirth is limited to shortening the period of pushing at the expense of episiotomy (epiziraphia). Analysis of the results of previous pregnancies and childbirth showed that in the anamnesis of a woman examined in a sufficient number in the main and comparative groups, there was a premature childbirth. In the comparison group, 30% had a premature childbirth delivery before the current pregnancy. Spontaneous miscarriage was reported in 33.3% up to 16 weeks, the pregnancy ended with a physiological childbirth delivery with only 5 pregnant women (16.6%) in the comparison group.

Analysis of the complications of previous pregnancies in the examined women showed that the risk of early toxicosis and miscarriage was one of the most common complications of pregnancy and was found in one in three women. It should be noted that in most observations, early toxicosis had a moderate course, the risk of miscarriage was significant and required inpatient treatment in 43.3% of cases (26 pregnant women from the main and comparison groups). The second most common complication was anemia in pregnant women, and it was also moderate nature. The third complication was swelling in one in two pregnant women according to the frequency of occurrence. Isthmic-cervical insufficiency was noted in 7 patients (4 pregnant women in the main group and 3 pregnant women in the comparison group), however, the diagnosis

has not been confirmed in the current pregnancy. There were 29 indications for caesarean section in 9 pregnant women, that is, 3.2 instructions fell to the share every pregnant woman.

17 babies (28.3%) were born in two groups. Evaluation of babies born to women over 35 years of age on the Apgar scale was above 8 / 8-8 / 9 in 8 (13.3%) observations. The condition of six babies was assessed as 6-8 points, the condition of 1 as 1 point. The mean weight was 2760 ± 124 g, and nine babies were underweight.

The course of the women gestation process in the selected groups, as well as the perinatal results were analyzed by us to assess the impact of ozone therapy of the clinic of the pathology of pregnancy.

In the analysis of women's extragenital diseases in the main and comparative groups, it was confirmed that there was no statistically significant difference in the main indicators (chart 1).

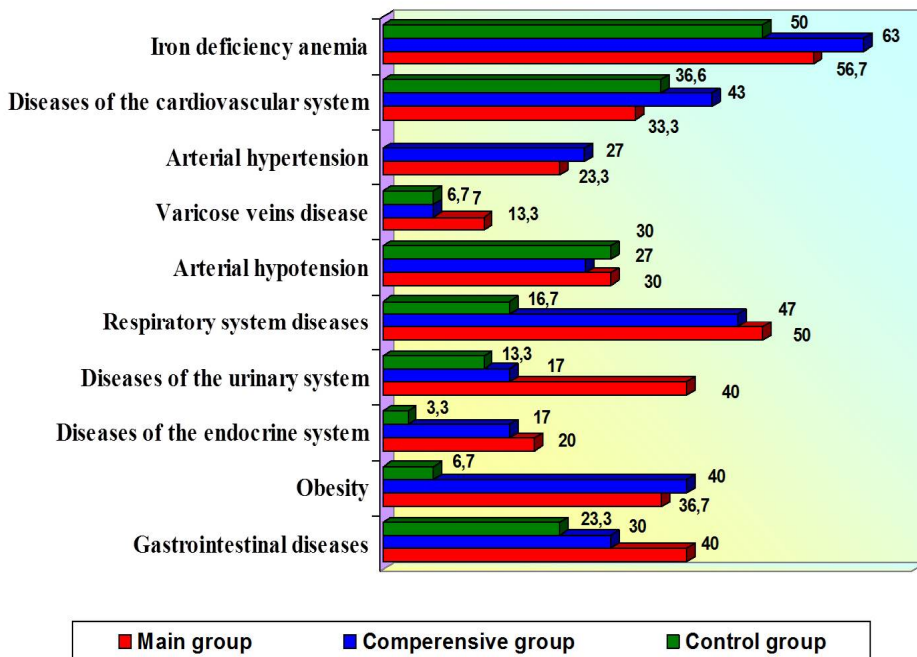


Chart 1. Structure of extragenital diseases in the studied groups

All women were registered for pregnancy before the 12th week of pregnancy and were fully examined in accordance with applicable orders and standards.

During previous pregnancies, 5 (16.6%) pregnant women in the main group and 6 (20%) pregnant women in the comparison group had complaints of high blood pressure from the 8-10th week of pregnancy.

The assigned diagnosis of high uterine tone was made in 29 pregnant women in the main group and 30 pregnant women in the comparison group mainly during palpation. Thus, signs of danger of pregnancy disorders were found in all pregnant women.

It should be noted that pathological conditions such as more than two complications, anemia of various degrees - 15 (50%), fetal growth retardation syndrome (23.3%), deficiency of fetoplacental complex - 17 (56.7%) cases have been reported in all women of the main group. As for the control group, all women's pregnancies had a physiological course, mild anemia was reported in 6 (20%) women, which was assessed by us as a physiological condition for a specific period of pregnancy.

In our study, the clinical signs of the risk of miscarriage appeared in all pregnant women of the main group and the comparison group at 12-22 weeks, i.e. in the second trimester.

In the second trimester, grade I-II edema was detected in 7 (23.3%) pregnant women in the main group and 9 (30%) women in the comparison group. Proteinuria was reported in 1 (3.3%) pregnant woman in the comparison group. Elevated blood pressure (arterial hyperstenuria) was noted in 4 (13.3%) pregnant women in the main group and in 6 (20%) women in the comparison group.

As a result, it should be noted that at the beginning of ozone treatment, the clinical course of pregnancy did not differ by group and no statistically significant difference was obtained during the study.

A detailed analysis of the characteristics of the patient's release was conducted to assess the impact of the course and outcome of the childbirth. Spontaneous childbirth occurred in 66.7% of cases among

patients of group I and in group I, 26.7% cases in group II and 100% cases in the control group.

In the main and comparison groups, there was an increase in the frequency of premature births compared to pregnant women with physiological progression hestasis ($p<0,05$).

Childbirth delivery occurred with the presentation of the head (breech) in 17 out of 30 pregnant women in the main group (56.7%) and in 5 (16.7%) women pelvic delivery. Natural childbirth delivery is more common in women in the control group than in the main group. Spontaneous labor was less common in women receiving standard therapy in the second trimester due to the risk of miscarriage ($p<0.05$).

The structure of cesarean section instructions did not differ between groups. As a matter of urgency, there were several simultaneous indications for caesarean section in both groups. The most common complication in the comparison group was deterioration of the fetoplacental system.

Early delivery period was largely uncomplicated in all groups. In the main group, 20 (66.7%) babies were born on time, and in the control group, 28 (93.3%) babies were born on time. The perinatal status of newborns was studied in all women.

The analysis was performed in the first and fifth minutes of the life of the newborn on the basis of clinical assessment of physical parameters, early neonatal period on the Apgar scale. The average body weight of infants born at 36-40 weeks of gestation was 3251 ± 24.5 g in the main group, which is higher than in the comparison group - 2860 ± 46.5 g. In the control group, this indicator was 3450.5 ± 52 g.

There is also a significant difference in the body length of infants - 49.6 ± 0.19 cm compared to 51.72 ± 0.18 cm. In the control group, this indicator was 52.26 ± 0.5 cm. In the 1st minute, the average score on the Apgar scale averaged 7.64 ± 0.42 points in the main group and 7.05 ± 0.18 points in the comparison group. In the 5th minute, this indicator was 8.94 ± 0.34 in the main group and 7.24 ± 0.26 in the comparison group.

The data presented confirm that perinatal diseases were more common in newborns in the comparison group. In the comparison group, 11 (36.7%) of the newborns had early neonatal: in 9 (30%) - asphyxia at birth, in 1 (3.3%) - meconial aspiration, in 1 (3.3%) - cephalohematoma. At this time, 8 (16.7%) infants from the comparison group and 6 infants from the main group were transferred to the intensive care unit, 9 (30%) infants from the comparison group were transferred to the intensive care unit, as a result, they were all discharged home in satisfactory condition. There were no perinatal deaths in our study.

Summing up the above, it should be noted that a comprehensive examination of older pregnant women who received complex treatment during pregnancy, including ozone therapy shows that thanks to the given non-drug methods of treatment, the following indicators have improved: course of pregnancy on clinical-laboratory, physical development, adaptation-defense reactions and the baby's condition on perinatal disease parameters, the course of the birth act and the postpartum period.

As the gestation process came to an end, the analysis of the course of labor showed that a large number of pregnant women over the age of 35 belong to the high risk group for complications. As a result, already in the pregravidal period, detection of risk factors for the normal course of pregnancy and optimizing the tactics of pregnancy and childbirth in women are necessary.

All fetuses at 10-14 weeks of age were screened by USM in the first trimester of pregnancy. In the control group, 28 (93.3%) pregnant women conformed to the normative values for the period of fetal BMI, and only 2 (3.7%) noted an increase in BMI in the fetus, which is probably due to constitutional features. No decrease in fetal BMI was noted. However, in the main group and the comparison group, only 12 (40%) and 10 (6%) pregnancies were found to correspond to the gestational period. At the same time, a decrease in this indicator was noted in 14 (46.7%) patients in the main group, 15 (50%) patients in the comparison group. That is, fetoplacental insufficiency is manifested primarily in the first trimester with a decrease in BMI.

Under the influence of metabolic disorders and hormonal changes during FPI, the nutrition of the fetus in the placenta is impaired, and IUGR is formed.

The development of the fetus was observed and its size was determined by us in the second USM screening by fetometry at 20-25 weeks. The mean values of the biparietal scale (BPS) corresponded to the normative values in the control group at 20-21, 22-23 and 24-25 weeks. BPS was significantly lower in the 24-25 week period than in the main and control groups ($p < 0.05$), indicating that IUGR had already developed in the second trimester of pregnancy.

Significant dynamics great dynamics were revealed compared to BPS indicators, in the indicators of the fetal abdominal circumference. Compliance with the term, was observed in 21 pregnant women in the main group and 29 women in the control group, and only 13 women in the comparison group. It was also noted in 11 (36.7%) women in that group.

Hip bone length was within the normative values for the period of gestation in 21 (70%) fetuses in the main group, its decreased was observed in 6 (20%) fetuses and increased in 3 (10%) fetuses. However, in the comparison group, a decrease in the length of the hip bone was observed in 11 (36.7%) fetuses, i.e. there is a big difference.

US markers of deficiency of cord not detected, low water content in 5 (16.7%) patients, hypoplasia of cord in 7 (23.3%) patients, that is, a decrease in the thickness of the cord relative to the period of gestation, small calcinates in the parenchyma of the cord in 9 (30%) patients, high water content in 4 (13,3%) patient were observed in 12 (40%) women observed in the main group. However, it should be noted that in 11 (36.7%) cases, several unfavorable factors were simultaneously, and in 2 pregnant women, three factors were noted together - excessive hydration, hypoplasia and calcifications.

In the comparison group, these indicators were negative in a large number of pregnant women. No signs of fetoplacental insufficiency were found only in 4 (13.3%) women. High water content was found in 9 (30%), low water content in 11 (36.7%) women, hypoplasia of the cord was found in 40% (12) women, 18 (60%) - calcinates, some

of the ultrasound markers listed in 14 (46.7%) women were recorded together.

In order to assess the final informativeness of ultrasound fetometry, a detailed analysis of its results was performed in the 3rd trimester of pregnancy. The results of the latter were evaluated by us during several studies in dynamics.

The presence of calcinates in the cord was observed in 1 (3.3%) case in the main group. In all observations in the control group, the maturity of the cord was in accordance with the period, in half cases not in accordance with the term in the main group, its premature "aging" was noted, 24 (80%) did not meet the deadline in the observation in the comparison group. This time, there were its premature "aging", in 16 (53.3%) cases, and a case of morphofunctional immaturity in 8 (26.7%) cases.

Thus, in the 3rd trimester of pregnancy, the fetometric criteria in the control group are within the normative indicators, while in the main group and in the comparison group it lags behind the norms of gestation.

In concluding the given information, it should be noted that

Exographic signs of fetoplacental insufficiency found among pregnant women of the main group and the comparison group confirm the presence of chronic fetoplacental insufficiency. As a result of complex treatment, including ozone therapy, the condition of both the placenta and the fetus improves.

In recent years, there has been a strong interest in dopplerometric examination of the circulatory system in the uterine arteries because of circulatory disorders plays a key role in the pathogenesis of FPI and IUGR and significantly worsens the prognosis of the newborn's psychomotor development.

Two-phase curves with high diastolic velocity of blood flow were found by us during the registration of blood flow velocity curves in the uterine arteries of women with normal pregnancies, it is also characteristic of vessels with low peripheral resistance and is an indicator of morphological changes in the spiral arteries during the normal course of pregnancy.

A comparative analysis of maternal-placental-fetal circulation in women of late reproductive age showed that increase in vascular resistance indices and a decreased pulsation index in the middle cerebral artery of the fetuses of pregnant women is noted in the uterine arteries of pregnant women, in the umbilical artery. This indicates an increase in blood flow resistance in the vessels of the mother and fetus, a limited blood supply to the placenta and fetus, and, accordingly, the possibility of various disorders of the mother-placenta-fetal system (hypoxia, metabolic, structural disorders, etc.).

One of the methods to confirm the diagnosis of intrauterine hypoxia was antenatal cardiotocography.

Cardiotocography was performed from the 30th week of pregnancy until delivery. Mild degree of hypoxia (6-7 points on CTG) 160-170 tachycardia per minute, short-term monotony of rhythm (up to 50% of the note), weakening of the reaction was attributed to the tests. Pregnant women those found to be late deselerations or absence of deselerations were attributed to the bradycardia (less than 100 beats per minute) or tachycardia (more than 170 beats), monotony of rhythm, movement of the fetus during stress-free testing during the execution of KTQ to moderate (4-5 points) and severe (less than 4 points) hypoxia.

General clinical and biochemical blood tests were taken from all pregnant women when entering the hospital for treatment and registering at home. In addition, patients in the main group received a blood test after the end of ozone therapy, and pregnant women in the comparison group received a blood test within 21 days after the completion of outpatient treatment.

Post-treatment hemoglobin levels and erythrocyte counts were significantly higher compared with the level of these indicators before treatment ($p < 0.001$) and compared with pregnant women in study group II ($p < 0.001$).

As a result of a full course of treatment, the number of platelets increased by $68.3 \times 10^9/l$. Leukocyte count increased slightly without statistically significant differences.

There was no significant difference between the main group and the comparison group in the remaining data of the general clinical analysis of blood after the treatment.

Thus, the inclusion of ozone therapy in the course of treatment of pregnancy risk allows to significantly improve the laboratory parameters of blood serum of pregnant women.

It is important to study the hormonal balance during gestation, because hormones of the fetoplacental system are important for the normal functioning of hormonal homeostasis during pregnancy (chart 2).

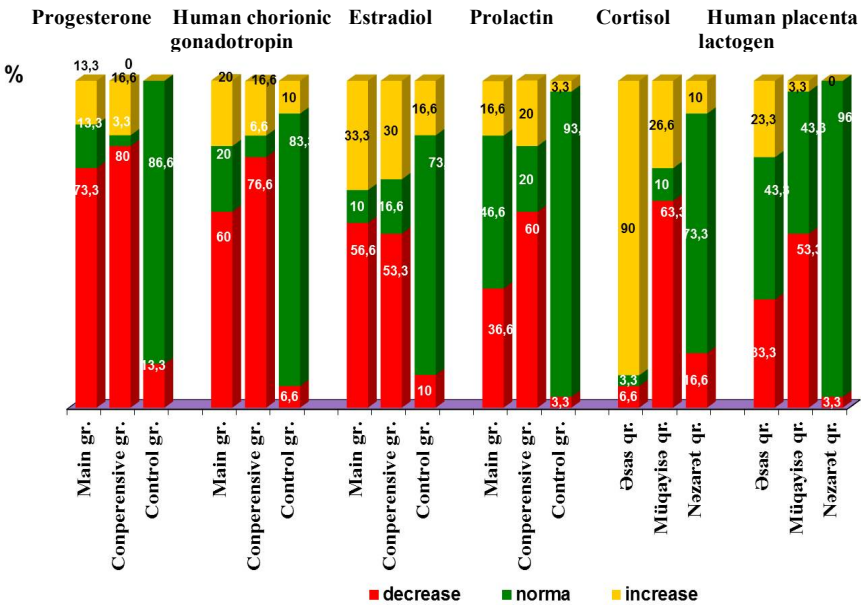


Chart 2. Levels of key hormones of the fetoplacental complex in the blood of pregnant women

Analysis of data on the levels of key hormones of the fetoplacental complex revealed a significant imbalance in most pregnant women in the blood of pregnant women belonging to the late reproductive system in the first trimester of gestation.

A characteristic feature of most pregnant women is the initial low level of progesterone in the blood. Low levels of this hormone were reported in 73.3% of cases in the main group and in 80% of cases in pregnant women in the upper age group. Only 4 (13.3%) women in the main group and 1 (3.3%) women in the comparison group have this hormone within the norm.

Determination of estrogen fraction levels in pregnant women also revealed abnormalities. Decreased estradiol concentrations were reported in 56.6% of cases in the main group and 53.3% in the comparison group. The normative price is typical for 22 (73.3%) pregnant women in the control group, the norm was reported 3 (10%) cases in the main group, and 5 (16.6%) cases in the comparison group.

In the study of placental lactogen, abnormalities were found in 10 (33.3%) pregnant women in the main group and 16 (53.3%) women in the comparison group. The norm was recorded in 43.3% (13) women in the main group and 43.3% (13) women in the comparison group. In the control group, normative indicators are recorded in 96.6% of cases.

In our study the concentration of human chorionic gonadotropin in the main and comparative groups is much lower than normal.

The performed study showed a statistically significant change in cortisol levels in the pregnant women examined. In the main group, cortisol levels were high enough in 27 (90%) pregnant women, and low in 2 (6.6%) women. In the comparison group, cortisol decreased in 19 (63.3%) patients and increased in 8 (26.6%) patients.

Prolactin concentrations were within the normal range in most pregnant women in the main group (14-46.6%). In the comparison group, 18 (60%) women were high and 6 (20%) women were low.

In the main group of pregnant women in the second trimester, blood progesterone was 16.6 ± 0.34 , which is 3.2 times higher than the level of progesterone in the first trimester, and 1.1 times higher than in the comparison group. The increase in progesterone was 3.5 times higher than the initial data in patients receiving ozone therapy in the third trimester of gestation and compared to pregnant women in the comparison group was 1.1 times higher.

According to the clinical protocol of the Ministry of Health of the Republic of Azerbaijan dated 2012, the indicator of progesterone in the II trimester was 4.14 ± 0.46 , and in the III trimester it was 18.09 ± 0.37 during drug therapy in the comparison group.

Studies of estradiol in pregnant women in the control group showed a steady increase in dynamics from 572.4 ± 1.57 to 16650 ± 1921.37 . This indicator was 314.37 ± 5.32 in the second trimester and 463.73 ± 13.68 in the third trimester in pregnant women from the main group. That is, E2 increased 1.1 times in the second trimester and 1.6 times in the third trimester.

In the group of pregnant women treated with traditional methods, E2 levels increased slightly compared to the initial indicators and amounted to 237.17 ± 5.29 , 270.87 ± 2.73 in the second trimester, and 297.8 ± 2.31 in the third trimester. In the main group of pregnant women, the concentration of placental lactogen at 22-24 weeks was 2.86 ± 0.07 . Placental lactogen levels were 2.35 ± 0.33 in the comparison group.

Placental lactogen levels increased accurately and were 4.60 ± 0.6 , while placental lactogen in the comparison group was 3.94 ± 0.94 in the third trimester, at 33-34 weeks.

During the study of prolactin levels in the first trimester in pregnant women from the main group and the comparison group as well as a significant decrease was found in the main group and in the comparison group - 25.03 ± 0.45 , 18.45 ± 0.45 , respectively. In the control group, this indicator was 74.5 ± 2.22 , which characterizes the norm.

Re-determination of prolactin in the blood showed that hormone levels increased slightly to 31.76 ± 0.61 among the pregnant women in the main group. In the third trimester, this indicator was in accordance with the normative data and was at the level of 142.48 ± 0.59 , which is 5.6 times higher than in the first trimester, 4.05 times higher than the average prolactin in pregnant women in the comparison group.

Analysis of the dynamics of prolactin secretion in pregnant women from the comparison group did not reveal significant differences in the background of conventional therapy.

Concentration of chorionic gonadotropin in the blood serum in the main group of pregnant women after ozone therapy was 17233.33 ± 144.09 in the second trimester and 25596.67 ± 173.49 in the third trimester. The mean amount of chorionic gonadotropin in pregnant women in the comparison group increased slightly after treatment - in the II trimester - 16853.33 ± 166.76 , in the III trimester - 18713.33 ± 135.59 .

Pregnant women belonging to the upper age group are initially in a state of chronic psycho-emotional stress, which leads to the production of excess stress hormones in the mother's body, especially cortisol and prolactin.

This indicator fell to normal according to the period of gestation in the second trimester, in the main group, however, mean levels of the hormone remained high in the comparison group. The same ratio is observed in the third trimester, which may be the reason for premature birth.

Thus, the use of ozone therapy as part of complex therapy in the treatment of fetoplacental insufficiency in women of late reproductive age has shown its high effectiveness in terms of improving clinical, biological and hormonal parameters.

RESULTS

1. Analysis of data on concomitant pathology showed that the most common pathologies in women of the main and comparative groups are iron deficiency anemia (56.7% and 63.5%) and diseases of the respiratory system (50.0% and 46.7%). Analysis of gynecological diseases by groups showed that endometriosis in 16.6% of the main group, in 10% of the comparative group, endometritis - in 13.3% and 10%, respectively, mastopathy - in 10.0% each, myomas - each was 3.3%. Signs of neuroendocrine syndromes - premenstrual syndrome - were noted in the majority of women in the main and comparative groups (60% and 70%, respectively). In the control group, this indicator was 10% [3, 10].

2. The most common complications were premature opening of amniotic fluid (35%), toxicosis (33%), preeclampsia (25%), risk of miscarriage (22%), and premature childbirth (17%) in pregnant women of late reproductive age. The risk of miscarriage is difficult to correct with medication and has become a risk factor for premature childbirth in women over 35 years of age. Early postpartum period was largely uncomplicated in all groups [3, 10].
3. It has been established that ozone therapy used in the complex treatment of fetoplacental insufficiency in women of late reproductive age has a positive effect on clinical, biochemical and hormonal parameters – on blood oxygenation and improves the blood supply of the cord, provides normalization of the function of the fetoplacental complex [1, 4, 7, 8].
4. The use of ozone therapy in the treatment of fetoplacental insufficiency in women of late reproductive age is pathogenetically justified – activates the fibrinolysis system by correcting hemostasis, reduces the level of hypoxia at the placenta, by improving placenta-fetus blood circulation which is reflected in the increase in the index of resistance and systolic-diastolic ratio to normal: umbilical artery resistance index increased by 21.9% ($p<0.05$) compared to the initial indicator; the systolic-diastolic ratio in the umbilical artery increased by 3-5% compared to the initial level ($p<0.05$) [1, 7].
5. Carrying out a set of treatment-diagnostic measures to correct uterine-cord blood circulatory disorders reduce the frequency of fetus of intrauterine growth retardation syndrome by 3.1 times ($p=0.001$), the frequency of delivery of babies those have hypotrophy by 3 times ($p=0.004$), and, reduces the frequency of children born with acute hypoxia by 9.6 times ($p=0.025$), also reduces perinatal mortality [2, 5, 6, 9].

PRACTICAL RECOMMENDATIONS

1. Pregravidity examinations, assessment of somatic status and reproductive system are recommended for late reproductive age

those have high somatic and gynecological diseases, aggravated obstetric history.

2. The medical and prophylactic measures recommended at the stage of women's counseling include the formation of a group on hestosis, intrauterine developmental disorders, anomalies of childbirth and postpartum period pathologies.
3. In order to increase the effectiveness of treatment and reduce perinatal pathology, women with placental insufficiency are recommended to include ozone therapy in the scheme presented in the complex treatment.

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The defense will be held on 31 March 2022 at 14⁰⁰ at the meeting of the Dissertation council ED.2.06 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at Azerbaijan Medical University.

Address: AZ 1022, Baku, A.Gasimzade str, 14 (meeting hall)

Dissertation is accessible at the Library of Azerbaijan Medical University

Electronic versions of dissertation and its abstract are available on the official website of Azerbaijan Medical University

Abstract was sent to the required addresses on February 2022.

Signed for print: 22.02.2022

Paper format: 60 x 84 1/16

Volume: 36200

Number of hard copies: 20