# FEATURES OF REPRODUCTIVE HEALTH OF WOMEN WITH LOW BIRTH WEIGHT AND OVERWEIGHT AT BIRTH

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**Abstract: The aim of the study** was to clarify obstetric and perinatal risk in women born with low or overweight.
**Materials and methods.** 343 women with birth weight abnormalities were examined. From them 3 groups are made, according to criterion "weight of the woman at a birth": I – 107 women with low weight at a birth, II – 126 with excess, III – 110 people with normal weight. The anamnesis, in particular, family and own perinatal, as well as nutritional support, anthropometric data, the structure of pregnancy complications, the rate of growth and development of the fetus, perinatal results were determined. Levels of eicosapentaenoic and docosahexaenoic acids were determined as markers of nutritional support of the organism, as indicators of angiogenesis were determined – concentration of vascular endothelial growth factor and placental growth factor in blood, morpho-functional studies of placenta were performed.
**Results.** Women born underweight are more likely to have menstrual disorders (every 4), infertility (every 10), miscarriage (every 5) and gynecological diseases. The pathology of gestation in such women and their mothers is similar in spectrum, which is an example of intrauterine programming. The implementation of this program is facilitated by negative factors of nutritional provision: inadequate breastfeeding, economical type of nutrition in favor of restricting protein foods and deviations in the process of angiogenesis.
**Conclusions.** The importance of perinatal history as a factor that determines the increased risk of menstrual disorders, the frequency of infertility, the pathological course of gestation during pregnancy, the predisposition to placental insufficiency and the birth of a child with low weight.
Women born with low birth weight and overweight are a contingent of increased perinatal risk, which is associated with a complicated own perinatal history on the background of obstetric pathology in their mothers. This fact complements the concept of intrauterine programming.
**Keywords:** low birth weight, macrosomia, reproductive health, nutritional deficiency.

## 1. Introduction

The demographic potential of society is inextricably linked with the impact of perinatal events on the quality of human health in the afterlife [1]. However, the understanding of the mechanisms of determination, implementation, modification of these influences remains limited.

The high and increasing in recent decades the frequency of births of children with deviations of the parameters of physical development from the limits of population standards leads to a comprehensive assessment of the long-term effects of these phenomena in the social and medical dimensions. Low birth weight (LW) due to intrauterine growth retardation (IUGR), as well as premature birth (PB) has proven negative consequences for human development, quality of health in the future, life expectancy [2, 3]. Babies who belong to the category of large fetus (LF), in addition to numerous abnormalities of hormonal and metabolic processes, often have traumatic injuries, are more likely to be born by cesarean section (CS) which also carries certain risks [4, 5]. Both variants of deviations of intrauterine growth parameters increase the chances of developing obesity, diabetes mellitus, arterial hypertension in the next life, which is due to the depletion of adaptation mechanisms in early ontogenesis, and hence the formation of hypothalamic-pituitary-adrenal axis dysfunction with irreversible negative consequences [6, 7].

The modern format of the *concept of intrauterine programming* leaves open questions concerning the state of the reproductive system. In particular, need to specify the features of women born with LW, as well as overweight, the relationship between their own perinatal health and components of reproductive function (menstrual, reproductive), the frequency and range of their disorders, pregnancy, development of the feto-placental system (FPS). Studying these connections, understanding their logic and patterns is an important condition for improving the concept of perinatal risk.

The aim of the research was to clarify obstetric and perinatal risk in women born with low or overweight.

## 2. Methods

343 women who were born from singleton pregnancies with different variants of birth weight deviation from the average were examined. Of these, there are three groups, according to the criterion of "woman's weight at birth": I – 107 women with LW at birth, II – 126 with excess, III (control) – 110 people with normal weight. The study was performed on the basis of the municipal non-profit enterprise "City Clinical Maternity Hospital No. 6" of the Kharkiv City Council during 2015–2018.

According to the conclusions of the Ethics Commission of the Kharkiv Medical Academy of Postgraduate Education (Minutes No. 2 of 22.10.2020), the study meets the ethical principles of scientific medical research with human rights, approved by the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human research object" (2008). All patients involved in the study were informed and agreed to participate.

The components of the examination protocol were a detailed family history, own perinatal history, formation and characteristics of menstrual function, gynecological pathology and its treatment, the course of previous pregnancies and births. Taste and nutritional habits before and during pregnancy, anthropometric data, weight gain during pregnancy, the structure of pregnancy complications, the rate of growth and development of the fetus, perinatal results were determined.

Somatogenetic analysis was used to evaluate the physical data, taking into account the syndrome of undifferentiated connective tissue dysplasia (UCTD), for the identification of which the M. Gleshbi scale (1989) was used to determine the degree of dysplastic changes according to the table of L. N. Fomina (2001).

Ultrasound (US) test was performed on Mindray DC-T6 (China) and Phillips HD11XD (Austria) scanners with transabdominal convex sensors with a wavelength of 3.5–5 MHz; vaginal sensors with a wave frequency of 8–10 MHz. Complex ultrasound included fetometry, cervicometry, Doppler FPS with assessment of blood flow in the uterine arteries (UA) of the right and left, umbilical arteries (UAr), middle cerebral artery (MCA), resistance index (RI), pulsation index (PI), with the definition of cerebro-placental ratio (CPR).

Levels of eicosapentaenoic and docosahexaenoic acids (EPA and DHA) were determined as markers of nutritional support

by gas chromatography. Indicators of angiogenesis – blood levels of vascular endothelial growth factor (VEGF-A) and placental growth factor (PlGF) – were determined by enzyme-linked immunosorbent assay.

Morpho-functional studies of manure included morphometry, histological and immunohistochemical methods.

When processing the material, the normality of data distribution was assessed by Kolmogorov-Smirnov. To compare the variables, the difference between the groups was assessed by mathematical methods of statistical data processing: variation, Student's criteria, $\chi^2$, Fisher, relative risk (BP) at 95 % confidence interval (CI), the reliability of which was determined at $p \leq 0.05$. We used licensed software ("STATISTICA", "EXEL").

### 3. Research results

In the course of a prospective study of sample groups in the study of family history, the peculiarities of perinatal development of women born with LW and LF were established. Thus, women of group I are characterized by the burden of their own perinatal history: the pregnancy of their mothers three times more often than the control had a complicated course ($p<0.01$) due to early toxicosis (16–14.9 %), the threat of abortion (18–16.8 %), anemia (27–25.2 %), placental insufficiency (PD) (14–13 %). In group II, the frequency and spectrum of maternal pathology were similar: early toxicosis – 18 (14.2 %), the threat of abortion – 15 (11.9 %), anemia – 39 (30.9 %), placental insufficiency – 16 12.6 %). Indications for complications of pregnancy preeclampsia (PE) in mothers of group I (8–7.4 %) were 4 times more frequent than in III (2–1.8 %) and twice as much as in II (4–3.2 %).

Our observations did not confirm the correlation between a woman's birth weight and mass growth parameters in the following. In addition, the total rate of "overweight + obesity" in groups I and II exceeds 25 %, which indicates a significant contribution of persons who in the perinatal period had disorders of trophic processes, in the formation of negative characteristics of the population.

It is noteworthy that the number of women in group I who received sufficient breastfeeding is twice less than in II and III (I – 36 (34 %), II – 92 (73 %), III – 76 (69 %), $p<0.01$).

Late menarche occurred in every 5th of groups I and II, against every 20th in group III ($p<0.05$), menstrual irregularities in every 3rd group I, every 4th group II, against every 11th in group III. A history of infertility was noted by 10 (9.3 %) women of group I, 10 (7.9 %) – II. Gynecological operations were performed on 14 (13.1 %) women of group I, 7 (5.5 %) – group II, 5 (4.5 %) of group III ($p_{I-III}=0.02$). In addition, the percentage of reborn women in the main groups is lower compared to the control ($p_{I-III}=0.02$, $p_{II-III}=0.05$), despite the same age composition.

A burdened reproductive history due to pregnancy loss and perinatal loss had a history of every 5th group I and every 9th group II, which is at least 4 times more common than III ($p_{I-III}=0.001$; $p_{II-III}=0.02$).

The common characteristics of groups I and II were a significant proportion of the threat of abortion: I – 32 (29.9 %), II – 25 (19.8 %), which is 2–3 times higher than the control (11–10 %). The highest incidence of anemia was in women of group II – 43 (34.1 %). Other types of gestational pathology were more common in group I: PE –18 (16.8 %), PD – 17 (15.8 %), dehydration – 18 (16.8 %), IUGR – 20 (18.6 %). In those born with LW, the combined form of PE prevailed against the background of chronic arterial hypertension, in the groups born with LF and with medium weight, "pure" forms of PE were noted.

When tracking the taste preferences of women with "polar" body weights at birth, we noted the dominance of the economical type of nutrition due to the protein component (meat, fish) among women of group I ($p<0.05$). The reduced content of total protein, urea, creatinine in the blood of group I pregnant women in comparison with groups II and III was consistent with this. Half of the cases of PD in group I occurred in women who ate protein once a week or less. In group II, the data on the consumption of protein products did not differ from III. Regarding fish consumption, there is a tendency to ignore seafood in all groups with the worst results in group I – 9 (8.4 %). In total, no more than 21 % of the total contingent reported regular consumption of fish. This is fully consistent with the low concentration of Ω-3 polyunsaturated fatty acids (PUFA): EPA in those born with LW was the lowest in comparison with other groups (in I 0.07±0.019 μg/ml, in II 0.11±0.031, in III 0.18±0.033 μg/ml, $p<0.05$).

We found that the concentration of VEGF in the blood of pregnant women of group I (25.6±3.94 pg/ml) is lower than in group III (36.9±6.6 pg/ml, $p_{I-III}<0.01$) , PlGF (respectively 0.8±0.25 MoM; 1.7±0.23 MoM; $p<0.01$). The difference between VEGF indicators of groups II and III (II – 32.3±4.97 pg/ml, $p_{II-III}<0.05$) is not significant. In group I, a direct correlation was found between the weight of the unborn child and the level of VEGF ($r=0.8$; $p=0.01$) and PlGF ($r=0.58$; $p=0.02$), a similar relationship not found in group II.

It was also of interest to clarify the growth rate of the fetus and hemodynamics of FPS. Studies have shown that the growth rate of the fetus in the three groups corresponded to the gestational age up to 30–32 weeks. For the first time, a slowdown in fetal growth was observed in all groups at the same time (34–36 weeks), but its frequency prevailed in group I – 4 times more often than in group II, and 10 times more often than in group III ($p<0.05$). In group II, the acceleration of fetal growth was more frequent than in group III ($p<0.05$). It should be noted the slow rate of placental migration in abnormal variants of its location in groups I and II, compared with III, which should be considered as a consequence of vascular insufficiency.

Hemodynamics in FPS of women of the main groups differed in the early onset of increased vascular resistance in the arteries (24–26 weeks) and a higher frequency of changes, compared with the control group. The mean Doppler indices had no significant differences by groups at 24–26 and 30–32 weeks. In general, every 6th from group I and every 9th from group II registered blood flow disorders in UA, which is 1.5–2 times more often than in group III. Increases in vascular resistance in UAr occurred in every 6th person born with LW. In general, in the main groups, higher RI values in UA and UAr and lower RI values of MCA and CPR, starting from 34–36 weeks, than in the control.

A distinctive feature of group I is the higher frequency of births of children with LW – both malnourished (19–17.8 %) and premature (8–7.5 %), compared with group III, in which malnutrition was born 6 times less (3–2.7 %, $p_{I-III}<0.001$), premature – 2.7 times less (3–2.7 %, $p_{I-III}=0.19$). LF – 18 (14.3 %) were born more often in group II, against 5 (4.5 %) in group III ($p=0.02$). The structure of indications for CS in the main groups is similar: the dominance of childbirth dystocia (I – 23.5 % and II – 23.1 %) and functionally narrow pelvis (I – 17.6 %, II – 38.5 %).

Morpho–functional studies of manure showed the tension of compensatory reactions in the villous chorion of the placenta in both main groups. This manifested itself in the highest number of all types of villi ($p<0.05$), their perimeter and plane;

enhanced vascularization of intermediate and terminal villi, strengthening their connective tissue skeleton, enhanced synthesis of interstitial collagen type III, increasing the stability of vascular basement membranes due to increased content of collagen type IV.

## 4. Discussion

The data showed the peculiarities of perinatal development of patients born with LW and LF, which are associated with a certain list of disorders of women's reproductive health. The short stature, which is quite common in women with LW at birth, on the one hand, probably reflects the phenomenon of perinatal memory [8] in the context of "economical" phenotype, and on the other hand, may be a contribution to epigenetic regulation and imprinting control in response to negative factors during maternal pregnancy [9].

The increased frequency of late menarche, menstrual disorders, infertility and gynecological operations in patients of the main groups unequivocally characterizes the greater vulnerability of women with abnormal birth weights in terms of neurohumoral regulation of the reproductive sphere. The facts in favor of the lower reproductive potential of this contingent agree with this.

The high proportion of threatened abortions in the main groups is a sign of endocrine disorders of the reproductive system. In general, the spectrum of pregnancy complications is mostly a recurrence in the mothers of patients with LW and LF at birth, which with some probability also reflects epigenetic labels as the basis of intrauterine programming [10].

Significantly lower concentrations of VEGF and PlGF in those born with LW were probably associated with pre-existing gestational pathology. The absence of a difference in VEGF values of groups II and III corresponds to the frequency of endothelial dysfunction due to the pathology of pregnancy among women born with LF. All of this, combined with the correlation between birth weight and growth factor levels invented in Group I, indicates profound congenital angiogenesis in those born with LW. Such disorders are manifested in an increase in the frequency of vascular endothelial abnormalities and related pregnancy pathology, which leads to a decrease in the weight of the newborn fetus [11].

The predominance of fetal growth retardation in patients of group I should be perceived as a realization of the phenomenon of fetal programming for the reproductive sphere, because during pregnancy – the load on the body – in those born with LW there is a restriction in fetal nutrition or PB, probably due to inherited inability to bear a child with good perinatal result [12]. Acceleration of fetal growth in group II is the opposite programmed scenario for the period of pregnancy of women – LF.

The increase in vascular resistance in UA and UAr in patients with LW and LF at birth is consistent with the frequency of PD and PE pregnancy complications in them and indicates the formation of a variety of chronic disorders, most pronounced among those born with LW. It is possible that the latter is justified by disorders in the system of angiogenesis.

The high frequency of birth defects in women with LW and LF at birth is due to the incomplete process of formation of the ancestral dominant. The increase in the proportion of functionally narrow pelvis has heterogeneous factors in groups – the predominance of short women with correspondingly narrowed pelvic size for group I and increased birth rate of LF in group II.

Morpho-functional studies of manure have proven the perinatal significance of low and high birth weight in women. The observed universal changes in placental tissue in those born with LW and LF can be considered a manifestation of intrauterine programming, because the detected abnormalities characteristic of PD-associated conditions had no clinical manifestations in any of the patients. The only thing in common is the fact of disharmonious fetal development, so the functioning of FPS on the verge of compensatory capabilities should be perceived as a manifestation of potentiation of processes in generations.

**Study limitations.** The results of the study obtained in the study of the population of Eastern European women are limited by its specific features, in particular, anthropometric characteristics at birth, as well as ethnic, socio-demographic and climatic conditions and others. All this does not allow you to freely extrapolate the data to other populations, without taking into account these factors.

**Prospects for further research.** The identified incidence of infertility in women with LW and LF at birth opens the prospect for research and development of separate protocols for the treatment of fertility disorders from the standpoint of proven vascular insufficiency.

## 5. Conclusions

1. Women who are born with low and overweight are a contingent of increased perinatal risk, this risk is associated with a complicated own perinatal history on the background of obstetric pathology in their mothers, reflecting the reality of intrauterine programming of reproductive pathology.

2. Born underweight and premature women are more likely to have menstrual disorders (every 4), infertility (every 10), they are vulnerable to neuroendocrine gynecological syndromes (PCOS – 6 (5.6 %)), tumors of the reproductive sphere (11–10.6 %), miscarriage (19–17.7 %).

3. Pathology of the gestational process in women born with LW and LF, and in their mothers is similar in spectrum and frequency: placental insufficiency 17 (15.8 %), preeclampsia 18 (16.8 %), the threat of abortion 32 (29.9 %). In mothers, respectively, 14 (13 %), 8 (7.4 %), 18 (16.8 %), which is a manifestation of intrauterine programming, and also determines the tendency to potentiate adverse factors in generations.

4. The implementation of this program is facilitated by negative factors of nutritional supply, starting with inadequate breastfeeding (not more than 36 (34 %)), as well as economical type of nutrition and taste preferences in favour of limited consumption of protein foods (36–33.6 %), affects the deficiency of polyunsaturated fatty acids (the content of eicosapentaenoic acid in the serum 0.07±0.019 μg/ml is 1.5 times lower than those born with average weight, $p<0.05$), accompanied by abnormal angiogenesis (concentration of VEGF 2.6 pg/ml is 1.5 times lower than those born with average weight, $p<0.01$).

## Conflict of interests

The authors declare that they have no conflicts of interest.

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