SYNDROME OF PLACENTAL INSUFFICIENCY IN PREGNANT WOMEN WITH OBESITY

Irina Savelyeva¹, Olga Shirokova², Elena Bukharova³, Elena Galyanskaya⁴, Irina Polyanskaya⁵, Elena Krasnikova⁶, Nataliya Nosova⁷

¹,²,³,⁴,⁵,⁶,⁷ Omsk State Medical University

¹saveljeva_IV_omsk@mail.ru, ²olga-v.shirokova@mail.ru, ³Buxarova88@mail.ru, ⁴galyanskaya@mail.ru, ⁵Irpol19@mail.ru, ⁶Krasnikova-omsk@mail.ru, ⁷Natalya-nosova-85@mail.ru

Corresponding Author: Irina Savelyeva

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Abstract

Researchers interest to the problem of extra genital diseases in mothers has increased during the past years. Obesity rate worldwide achieved the level of one of the most significant problems in XXI century.

The Purpose of the Study: Evaluation of placental insufficiency syndrome risk development in pregnant women with obesity.

Materials and Methods: Prospective controlled study enrolled 494 patients. The 1st group included 262 patients with obesity (mean body weight index 33.1 (31.4; 35.9) kg/m²), aged 30 (27; 34) years old. The 2nd group (control) included 232 patients with normal body weight (mean body weight index 22.6 (21.0; 23.8) kg/m²) aged (25; 31.5) years old. The authors evaluated anthropometric data, conducted coagulotests, assessed lipid and carbohydrate metabolism, performed fetometry and Dopplerometry. All the patients had their level of human placenta growth factor identified (PlGF, pg/ml) in blood serum. Morphological study of secundines was conducted.

Results. It was defined that pregnant women with obesity had low level of P1GF in comparison with the women in the control group (p<0.01). Critical level of P1GF in prognosis of placental insufficiency development is considered to be lower than 100 pg/ml. Morphological study of secundines from delivered women with obesity showed significantly higher rate of placenta maturation disorders at low level of P1GF.

Conclusion: In pregnant women with obesity the level of P1GF on the 8-9th week of gestation was lower in comparison with the control group. The level of P1GF lower than 100 pg/ml at obesity in mother is considered as a marker of placental insufficiency development risk, which is confirmed by the morphological study of secundines.

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I. Introduction

Researcher’s interest in pregnant women obesity has increased during the past years [II, VI, IX, X, XI, XV, XVII]. Obesity rate increase worldwide reached the level of one of the most significant problems in XXI century. It is considered that pregnant women with obesity are at risk of preeclampsia, placental insufficiency and massive obstetric bleeding development [XVII, XXIII, XXIV, XXVI, VII, XXII]. However, there is lack of research data on the level of placental growth factor (PlGF), which is one of the main regulator of placenta development and placental villi vascularization [XXIV, XIII, XIX] in pregnant women with obesity. At present, an increasing number of researchers believe that the period of placental insufficiency (PI) formation is the time when cytotrophoblast migrates with the development of second invasion wave insufficiency [VII, IV, XIV, I], which corresponds with 8 – 9 weeks of gestation. The rationale for the present study is to evaluate the association between PlGF levels in the beginning of gestation period (8 – 9 weeks) in pregnant women blood serum and obesity, and between clinical picture of placental insufficiency and morphological peculiarities of secundines, because placental development disorders influence on its functional activity [XXII, VIII, XVI, V, XXI, XX, XII].

Purpose of the study is to evaluate the risk of placental insufficiency development in pregnant women with obesity.

II. Materials and Methods

Prospective controlled study included 494 patients. The 1st group included 260 patients with obesity aged 30 (27; 34) years old with mean body weight index 33.1 (31.4; 35.9) kg/m². The 2nd group included 232 patients with normal body weight aged 28 (25; 31.5) with mean body mass index 22.6 (21.0; 23.8) kg/m².

Study entry criteria:
- obesity in pregnant woman (for group I);
- absence of extragenital diseases decompensation (for all groups);
- participant consent (for all groups).

Study exclusion criteria (for all groups):
- multiple and Rh-incompatible pregnancy;
- extragenital diseases decompensation
- participant consent withdrawal.

The study was approved by Omsk State Medical University Ethical Committee decree № 97 dated 12.10.2017.
Methods of investigation included general clinical and laboratory tests for estimation of body mass index (BMI), waist circumference (WC), systolic BP (SBP) and diastolic BP (DBP). Levels of cholesterol (CL), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), plasma glucose, creatinine, uric acid were identified by biochemical assays. All patients had their level of human PIGF (pg/ml) in blood serum identified by immunological assay Quantikine Human PIGF (R&D Systems, USA), based on solid phase enzyme-linked immunosorbert assay (ELISA). At the same time, the authors conducted morphological study of secundines, which started with thorough macroscopic examination in labor ward right after delivery. The material was fixed in 10% solution of neutral formaline. Paraffin sections were Van Gienson stained with haematoxylin-eosin and picrofuchsin. To keep the groups consistency, the authors examined secundines obtained only after full-term pregnancies.

Statistical analysis was performed by software package Microsoft office 2007 (USA) and Statistica 10.0 (USA). The level of significance was taken as p<0.05. At normal data distribution, the mean value with standard deviation was estimated. At non-normal data distribution, median (Me) and interquartile interval was estimated (25; 75). Chi-square ($\chi^2$) for four-fold table (at p<0.05 critical value $\chi^2=3$, 841459) was used for calculation of statistically significant qualitative differences. Quantitative parameters were compared by Mann-Whitney test.

III. Results

The present study was aimed at attempt to identify prognostic associations between PI development in pregnant women and obesity, based on PIGF level change, and formation of placental insufficiency. The evaluation of human PIGF level in blood serum of pregnant women from group I and II showed that in pregnant women with obesity the level of PIGF was slightly lower (p<0.01) than in the control group, Table 1. This fact indicates on disorders in chorionic villi invasion processes and formation of insufficiency in trophoblast second wave invasion under low level of PIGF in 1 trimester.

Based on the identified levels of PIGF, the main group was divided into two subgroups: 1A – with high level of PIGF (n=87; Me 197.8 pg/ml; 128.7-303.2 pg/ml) and 1B – with low level of PIGF (n=175; Me 60.6pg/ml; IQS 22.9-80.0 pg/ml), Table 1. By the development of PI, the subgroups were divided additionally into 1A1 (high level of PIGF, PI was not diagnosed), n=59 and 1A2 (high level of PIGF, PI was diagnosed), n=28; and 1B1 (low level ofPIGF, PI was not diagnosed), n=31 and 1B2 (low level of PIGF, PI was diagnosed), n=144, Table 1.
Table 1: Level of PI GF in pregnant women blood serum in the test groups

| Patients Groups Parameter | Pregnant women with obesity (Group I), n=262 | Mann-Whitney test | Healthy pregnant women (Group II), n=232 |
|---------------------------|---------------------------------------------|-------------------|------------------------------------------|
|                           | Me   | IQS               | Me   | IQS           |                                  |
| PI GF (pg/ml)             | 71.2 | 31.1-181.2        | p=0.00068*     |                              |
| group IA, n=87            | 197.8| 128.7-303.2       | p=0.00017*     | 251 | 198.0-321.0 |
| group IB, n=175           | 60.6 | 22.9-80.0         | p=0.00018*     |                              |

Note* - the difference is statistically significant in comparison with the control group.

According to the authors’ data, the critical level of PI GF in the prognosis of PI development is below 100 pg/ml. Chronic PI was clinically and morphologically diagnosed in 172 (65.6%) out of 262 women with obesity, Table 2. Intrauterine growth restriction syndrome (IGRS) was diagnosed in 51 (19.5%; \( \chi^2 = 50.4; \chi^2 > \chi^2_{crit} p<0.05 \)) pregnant women with obesity. Dopplerometry results showed that 127 (48.5%; \( \chi^2 = 151.4; \chi^2 > \chi^2_{crit} p<0.05 \)) pregnant women with obesity had reduced fetoplacental perfusion. Along with this, in III trimester et al cardiotocographic examination was performed, which showed that 78 (29.8%; \( \chi^2 = 82.0; \chi^2 > \chi^2_{crit} p<0.05 \)) pregnant women with obesity had signs of fetal hypoxia. There were no cases of PI registered in the control group. Based on the fact that there was high rate of PI development in the main group of the examined women, the authors suggested that PI GF can be considered as a marker of PI development in pregnant women with obesity.

Clinicopathologic analysis of 262 secundines, taken from delivered women with obesity, showed that these patients had placenta development disorders more often than in the control group. Only 30 (11.5%; \( \chi^2 = 28.3; \chi^2 > \chi^2_{crit} p<0.05 \)) secundines did not have significant morphological differences from the control, Table 3. MePI GF in this group was equal to 155.9 pg/ml (IQS 69.3-256.0 pg/ml). Clinical symptoms of placental insufficiency were not registered either.
Table 2: Dependence of placental insufficiency development risk in pregnant women from the test groups on the level of placental growth factor

| Groups of the examined women | Placental insufficiency (n // χ^2) |
|------------------------------|-----------------------------------|
|                              | Clinical diagnosis                | PI morphological diagnosis |
|                              | IGRS                             | Fetoplacental perfusion disorder | Fetal hypoxia |
|                              | 51 // 50.4                       | 127 // 151.4                  | 78 // 82.0 |
|                              | IА 1, n=59                       |                                |               |
|                              | IА 2, n=28                       | 10 // 27.5*                   | 19 // 53.9*  |
|                              |                                 | 26 // 75.5*                   | 28 // 81.9*  |
|                              |                                 |                                |               |
|                              | IВ 1, n=31                       |                                |               |
|                              |                                 |                                |               |
|                              | IВ 2, n=144                      | 41 // 60.4*                   | 59 // 91.5*  |
|                              |                                 | 101 // 178.1*                 | 144 // 295.4*|
|                              | Control group=232                |                                |               |

Note*: statistically significant differences in comparison with the control group.

232 (88.5 %; χ^2=387.3; χ^2>χ^2 cratp<0.05) secundines had different forms of development disorders. Villi pathologic underdevelopment was registered in most cases – 119 (45.4%; χ^2=138.8; χ^2>χ^2 cratp<0.05), Figure 1. Cotyledons with premature placenta development and significant sclerotic processes were identified in 58 (22.1 %; χ^2=58.2; χ^2>χ^2 cratp<0.05) delivered women with obesity. Delayed placenta and dissociated cotyledons development was registered in 32 (12.2 %; χ^2=30.3; χ^2>χ^2 cratp<0.05) and in 23 (8.8 %; χ^2=21.4; χ^2>χ^2 cratp<0.05) secundines of the delivered women from the main group, Table 3.

![Figure 1](image)

Fig. 1: Villi pathologic immaturity in pregnant women, x400, H-E.
Morphological chronic PI was confirmed in 65.6 % of delivered women with obesity (Figure 2), and statistically more often ($\chi^2=64.7; \chi^2 > \chi^2_{crit, p<0.05}$) this complication was observed in delivered women with obesity with low level of PI GF, Table 2.

**Table 3**: Forms of development disorders in secundines of the delivered women in the tested groups

| Form of placenta development disorder | Groups (n // % // $\chi^2$) | Main group n=262 | Control group n=232 |
|--------------------------------------|-----------------------------|-------------------|---------------------|
|                                      | Low PI GF level n=175       | High PI GF level n=87 |
| Correlates with gestation age         | –                           | 30 // 34.5 // 88.3* | 232                 |
| Pathologic immaturity                 | 91 // 52.0 // 155.4*        | 28 // 32.2 // 81.9* | –                   |
| Premature development of placenta and significant sclerotic processes | 34 // 19.4 // 49.2*        | 24 // 27.6 // 69.2* | –                   |
| Villidelayed development              | 27 // 15.4 // 38.3*         | 5 // 5.7 // 13.5*  | –                   |
| Dissociated development of carydelons | 23 // 13.1 // 32.3*         | –                  | –                   |

Note*: differences are statistically significant in comparison with the control group.

Significant structural changes developed also in fetal membranes (induration and thinning of compact layer due to overgrowth of collagen fibers) and in umbilical cord (perivascular sclerosis and blood vessel walls thickening with significant luminal occlusion and collagen fibers appearance in muscle tissue).
It should be noted that the degree of structural changes, in general, and sclerotic changes, in particular, in fetal segments and umbilical cord directly depended on the character of similar changes in villous chorion. The most evident changes were observed in the group of delivered women with low level of PlGF.

IV. Discussion

The present study results confirmed the accepted fact that primary PI significantly more often developed in patients with extragenital pathology [II, XVII, XXIII, XIII, I, VIII, XXV, III]. Morphological study of secundines from delivered women with overweight showed significantly higher rate of placental disorders development in the subgroup with low level of PlGF in comparison with the subgroup of delivered women with obesity and high level of PlGF, p<0.05.

During the past years, researchers published data, based on growth factors studies, on possible prognosis of PI development at early stage of pregnancy under endothelial dysfunction appeared. Thus, clinical researchers acknowledge the importance of endothelial factor (VEGF) that dilates vessels in high concentrations and constricts them in low concentrations. Placental growth factor PlGF belongs to the family of vascular endothelial growth factor VEGF and acts as one of the main regulators of placenta formation and villi vascularization [VI, X, XVIII, IV, XXI, III]. However, the level of PlGF was not considered as a prognostic criterion in previous studies. Still, clinical and morphological associations, identified in the present study, allowed the authors to suggest that low level of PlGF could be used as a prognostic criterion for placental insufficiency development. The lower PlGF level in I trimester, the earlier it is necessary to start the preventive treatment of severe gestational complications.
V. Conclusion

The results of the present study allowed the authors to suggest that low level of PlGF can be used as a prognostic factor for placental insufficiency development. The lower PlGF level in I trimester, the earlier it is necessary to start the preventive treatment of severe perinatal complications.

Recommendations. In outpatient conditions obstetrician-gynaecologists have to focus their attention on primary diagnostics of obesity in fertile women at planning pregnancy, especially, if these women are in a risk group (miscarriage and premature birth, children with low body weight and frequently sick children). The results of the present study confirm the necessity to recommend the test for placental growth factor evaluation in I trimester of gestation for pregnant women with obesity as a part of complex outpatient monitoring. Critical level of development of severe gestational and perinatal complications is at the concentration of PlGF 100 pg/ml. Severe gestational complications treatment should include principles of intensive therapy based on participation in the obstetrics program of obstetrician-gynaecologists, neonatologist and resuscitationists.

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