PREDICTORS OF DECOMPENSATED PLACENTAL INSUFFICIENCY AMONG WOMEN WITH CHRONIC INFLAMMATORY DISEASES OF UTERUS ADJUNCTS

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One of the leading factors of perinatal death rate is placental insufficiency. Influence of pre-clinical systematic changes in female organism, related to development of placental insufficiency, opens a perspective of verifying predictors of gestation complications according to screening research of biochemical and biophysical indexes – IL-6, IL-8, IL-10, PIGF, VEGF-A. The article analyses level and dynamic of change in levels of cytokines and growth factors in blood of pregnant women with chronic inflammatory pathologies of uterus adjuncts. Conclusions on possibilities to predict placental insufficiency at early stages of pregnancy are made.

Keywords: perinatal death rate, placental insufficiency, cytokines, factors of placenta growth

Regardless of the general trend towards growth in coefficient of total birth rate, its current level in Russia remains among that of countries with the lowest value of it [5]. This situation is significantly complicated by the fact that reproductive growth of women remains unsatisfactory. Besides, regardless of certain decrease in perinatal death rate, during recent years coefficient of perinatal death rate, according to the data of 2014, remains above 8 ‰ [5].

One of the leading factors in perinatal death rate is placental insufficiency. Perinatal death rate, related to delay in embryo growth (DEG) reaches 287 ‰ [9]. DEG is registered in one third of all cases (37 %) of antenatal embryo death [8]. It is known that neonatal death rate exists in direct correlation with birth body mass [7]. High perinatal death rate among such infants is related not only to prematurity, but also to placental insufficiency [6]. At the same time a special risk group is formed by children who combine prematurity and intrauterine hypotrophy. According to many authors, presence of intrauterine hypotrophy increases risk of unfavourable perinatal outcome significantly [1; 2; 3].

The main achievement of modern stage in studying pathogenesis of obstetrics complications is cardinal broadening of researchers' ideas on angiogenic imbalance and vessel disturbance that attend to early stages of placental insufficiency and associated gestational complications [10], especially for women with chronic inflammatory pathologies of uterus adjuncts.

One of the most important functions of cytokines in human organism is regulating ebryogenesis, foundation and development of immune system organs. Cytokines, produced by cells of placenta, play an important part in regulating survival and normal development of an embryo, as well as forming inborn and obtained immunity for protection against infections [4]. Besides, growth factors IL-6, IL-8 play a leading part in processes of embryo implantation and its further placentation. Revelation of pre-clinic system changes in woman organism, particularly related to development of placental insufficiency, opens perspective of verifying precursors of gestation complications according to screening research of biochemical and biophysical indexes. Reserves of decrease in severity level of gestational complications are predicting placental insufficiency and revealing its markers at early terms of gestation.

Work objective: define predictors of emergence of decompensated placental insufficiency among women with chronic inflammatory pathologies of uterine adjuncts.

Materials and methods of research

88 pregnant women were placed under observation. Average age of patients equaled 29.

Criterions of inclusion into programme of observation: early reception in female consultation, monocarpic pregnancy, chronic inflammatory pathologies of uterine adjuncts, and patient's approval of constant observation during the whole gestation period.

Depending on peculiarities of pregnancy flow and its outcome, women were divided into three clinical groups.

Contingent of the first group was formed of women with physiological flow and outcome of pregnancy. To the second group patients with chronic compensated placental insufficiency that had no effect upon embryo development, were referred. Contingent of the third group included patients with decompensated placental insufficiency: chronic intrauterine hypoxia, DED, and giving birth to children with delayed development (hypotrophy). Diagnosis of placental insufficiency was confirmed by morphological development of placenta.

Each group of women was tested with the following examinations: analysis of anamnestic data and detailed evaluation of pregnancy flow and delivery, presence and nature of complications, and also complete

clinical-laboratory inspection of blood with definition of laucoformula, triple ultrasound examination with doppleometry. On week 32 of pregnancy embryo condition was evaluated with cardio-current graph examination. After delivery morphological study of placentas was made.

Ultrasound examination was made in female consultation of maternity hospital № 2 (with apparatus "Mindray DC-7").

Prediction of placental insufficiency flow and definition of its markers among women with chronic inflammatory pathologies of uterine adjuncts at pre-clinic stage I and II was made via collecting blood samples and its examination with systems of immune-ferment analysis IL-6, IL-8, IL-10, PIGF, VEGF-A.

In order select the most informative indicators (predictors) of decompensated placental insufficiency development mathematical apparatus of ROC-analysis was used with evaluation of sensitivity and specificity of all values for the studies variables. Besides ROC-curves, the basic characteristics of each indicator were: area under ROC-curve (ROC-area), standard error of evaluating ROC-area (S.E.), probability of first type error in comparison between ROC-curve and reference line (p), and value of each indicator with the highest sensitivity and specificity.

Method of logistic regression was implemented (multiple regression with logit-transformation) in analysis of complex influence. Modeling was made with module "Nonlinear estimation" with function Quick logit regression of statistic application pack STATISTICA v. 10.0. Procedure of modeling initially included a set of the most significant predictor of all used ones. Then method of forward stepwise was used to select the second predictor and so on until classification power of model stopped to improve (according to criterion χ^2). As a result of implementing this modeling method logistic classification models of evaluating probability of placental insufficiency risk were received.

Results of research and their discussion

In prediction of placental insufficiency at early terms of pregnancy hypothesis of endothelial dysfunction according to studying growth factors represents certain interest. In this regard a great attention is paid to growth factors VEGF-A and PIGF that participate in endogenic regulation of angiogenesis.

We undertook evaluation of placental insufficiency development risk according to examination of women at the first and second trimester of pregnancy, as a result, such indexes as "sensitivity" and "specificity" for probable predictors of placental insufficiency were defined. Sensitivity characterizes part of marker carriers among women with placental insufficiency. Specificity characterizes part of healthy women who don't carry the marker.

It was revealed that the greatest significance in evaluating development of placental insufficiency as early as in the first trimester was registered for IL-6 $(0,99 \pm 0,01; \ p < 0,0001)$. At the same time we can conclude underline that sensitivity for point 36,6 pg/ml equaled 100 %, and specificity – 92 %.

Besides, the following predictors were revealed as possible. For PIGF sensitivity equaled 48 %, $(0,77 \pm 0,05; \ p < 0,0001)$. For IL-10 $(0,67 \pm 0,06; \ p < 0,006)$ at point 57,6 pg/ml sensitivity equaled 45 %, and specificity – 94 %. For WBC $(0,64 \pm 0,06; \ p < 0,05)$ at point $8,2 \cdot 10^9$ kl/l sensitivity equaled 70 %, specificity – 60 %.

In result of stepforward introduction procedure we received model, constructed upon values of IL-6, WBC, and concentration of serum albumen (Table 2). High values of IL-6 increase calculated values of placental insufficiency emergence risk, while increase in number of leucocytes and albumens has an opposite effect. The final values of statistic significance for the model of evaluating probability of placental insufficiency are characterized by $\chi^2 = 114,21; \ p < 0,0001$.

Table 1

Results of ROC-analysis for the examined variables at the first trimester of pregnancy

Probable predictor	Area under ROC-curve ± S.E.	p	Indicator value with max Σ	Sensitivity	Specificity
WBC	$0,64 \pm 0,06$	0,0284	8,2	70 %	60 %
ALBUMEN	$0,62 \pm 0,06$	0,0599	39,4	48 %	75 %
IL-6	$0,99 \pm 0,01$	0,0000	36,6	100 %	92 %
IL-8	$0,57 \pm 0,06$	0,2562	24,6	75 %	54 %
IL-10	$0,67 \pm 0,06$	0,0053	57,6	45 %	94 %
PlGF	$0,77 \pm 0,05$	0,0000	69,4	48 %	100 %
VEGF-A	$0,55 \pm 0,06$	0,3835	64,2	33 %	96 %

Table 2

Results of multiple logistic regression analysis among the examined women
in the first trimester of pregnancy

Characteristics of model	Const.B0	WBC	Albumen	IL-6
Estimate	–2,12	0,04	0,84	–0,79
Standard Error	8,36	0,48	0,50	0,43
t(84)	–0,25	0,09	1,67	–1,84
p-value	0,80	0,93	0,10	0,07
–95% CL	–18,75	–0,92	–0,16	–1,65
+95% CL	14,51	1,01	1,84	0,07
Wald's Chi-square	0,06	0,01	2,80	3,38
p-value	0,80	0,93	0,09	0,07
Odds ratio (unit ch)	0,12	1,05	2,32	0,45
–95% CL	0,00	0,40	0,85	0,19
+95% CL	2008840	2,74	6,31	1,07

Table 3

Specificity and sensitivity characteristics for logistic model of placental insufficiency probability
according to results of examining women in the first trimester of pregnancy

Revealed	Evaluation – PI	Evaluation – no PI	Sensitivity / Specificity
Placental insufficiency	40	0	100,0%
No placental insufficiency	1	47	97,9%

For verification model with apparatus of ROC-analysis its results were very demonstrative and shown high classification efficiency of the represented model (p < 0,0001).

Table one provides results of ROC-analysis for the tested variables in the second trimester of pregnancy. Is was revealed that the greatest significance in evaluating placental insufficiency development in the second trimester was registered for IL-6, (0,94 ± 0,02; p < 0,0001). At the same time, we can outline that sensitivity at point 46,2 pg/ml equaled 98%, and specificity – 81%. The next predictor from the point of statistic significance is IL-8 (0,86 ± 0,04; p < 0,0001). For IL-8 at point 44,9 pg/ml sensitivity equaled 70%, and specificity – 90%.

Table 4

Results of ROC-analysis for the studied variables in the second trimester of pregnancy

Probable predictor	Area under ROC-curve ± S.E.	p	Index value with max Σ	Sensitivity	Specificity
PLT	0,66 ± 0,08	0,0518	249,0	50%	82%
ИЛ-6	0,94 ± 0,02	0,0000	46,2	98%	81%
ИЛ-8	0,86 ± 0,04	0,0000	44,9	70%	90%
ИЛ-10	0,59 ± 0,06	0,1471	42,3	93%	25%
PlGF	0,53 ± 0,06	0,6875	247,5	60%	52%
VEGF-A	0,51 ± 0,06	0,8834	76,7	28%	85%

Table 5

Results of multiple logistic regressive analysis among the examined women
in the second trimester of pregnancy

Characteristics of model	Const.B0	IL-6	IL-8
Estimate	4,626217	–0,02745311	–0,06545921
Standard Error	1,035773	0,01029411	0,02311393
t(85)	4,466441	–2,666875	–2,832025
p-value	2,4323E-05	0,0091644	0,005773728
–95 % CL	2,566823	–0,04792056	–0,1114159
+95 % CL	6,68561	–0,00698566	–0,01950254
Wald's Chi-square	19,94909	7,112225	8,020366
p-value	7,9804E-06	0,007659854	0,00462831
Odds ratio (unit ch)	102,127	0,9729203	0,9366372
–95 % CL	13,02439	0,9532095	0,8945667
+95 % CL	800,7993	0,9930387	0,9806864
Odds ratio (range)		4,244E-07	6,56561E-13
–95 % CL		7,53378E-12	1,84E-21
+95 % CL		0,02390766	0,000234612

Table 6

Characteristics of specificity and sensitivity for logistic model of placental insufficiency
probability according to results of examining women in the first trimester of pregnancy

Revealed	Evaluation – PI	Evaluation – no PI	Sensitivity / Specificity
Placental insufficiency	45	3	93,8 %
No placental insufficiency	9	31	77,5 %

As a result of implementing procedure of stepforward inclusion we received the best model, constructed upon values of IL-6 and IL-8 (Table 5). We should outline that increase in level of the mentioned cytokines increases probability of placental insufficiency. The final values of statistic significance for model of evaluating placental insufficiency probability is characterized by $\chi^2 = 61,41$; $p < 0,0001$.

After verifying the model with apparatus of ROC-analysis its results proved to be quite demonstrative and shown high classification efficiency of the presented model ($p < 0,0001$).

Conclusion

Thus, it was established that for the first trimester among all possible predictors of placental insufficiency the greatest significance belongs to IL-6, PIGF, IL-10. Increase of IL = 6 above 36,6 pg/ml, PIGF above 69,4 pg/ml, IL-10 above 57,6 pg/ml in blood serum of patients during the first trimester of pregnancy can help us reveal risk of placental insufficiency development among them.

For the second trimester to reveal risk of clinically-significant placental insufficiency among pregnant women with chronic inflammatory diseases of uterine adjuncts predictors IL-6 (46,2 pg/ml), IL-8 (44,9 pg/ml) proved

to be the most reliable. Correspondingly growth in levels of IL-6 and IL-8 above the mentioned values can indicate risk of decompensated placental insufficiency development.

The presented conclusion defines the necessity to develop algorithm of predicting placental insufficiency at the stage of pregravidary preparation and in early terms of pregnancy. These studies can serve as perspective directions of further work on the researched topic.

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