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COMPARATIVE ASPECTS OF PLACENTAL DYSFUNCTION IN WOMEN USING DIFFERENT METHODS OF CONTRACEPTION IN ANAMNESIS

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Abstract

The aim. To reduce the incidence of perinatal pathology in women who have used various methods of contraception, based on the study of the functional state of the fetoplacental complex (FPS), as well as improving diagnostic measures and tactics of pregnancy.

Materials and methods. 140 pregnant women were studied with their division into control and 3 test groups depending on the method of contraception in the anamnesis, using clinical, laboratory and instrumental research methods during pregnancy and childbirth.

Results. The study found that women with a history of intrauterine contraception (IUC), in contrast to combined oral contraception (COC) and combined oral contraception containing folate (COC+F), had a higher incidence of complications during pregnancy and childbirth, as well as fewer newborns with a satisfactory condition at birth. Assessment of folic acid levels at 6-8 weeks of gestation showed significantly better results among women with a history of COC+F, compared with IUC and COC. In the group of women with IUC in the anamnesis, significantly worse mean endocrinological values prevailed, and there was also a greater number of pregnant women with disorders of fetal-placental blood flow. More pronounced dystrophic changes in the placentas of women in this group were pathomorphologically confirmed.

Conclusions. The presence in the anamnesis of IUC is accompanied by a high proportion of pregnant women with various pathological conditions and is a risk factor for FPS dysfunction. The use of COC+F in the anamnesis is the best option for women of different risk groups.

Keywords: condition of fetoplacental complex, contraception, combined oral contraception, intrauterine contraception, folate.

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1. Introduction

Disturbance in the functioning of FPS leads to the formation of placental dysfunction (PD) and complications such as fetal distress, fetal growth restriction (FGR), increased perinatal morbidity, etc., subsequently causing underdevelopment of the central nervous system, high incidence in early and late neonatal periods and more [1, 2]. Among the potential causes of such violations, in addition to the generally accepted [3, 4], also highlight modern features in family planning, namely – the use of different methods of contraception. Despite the progress in its improvement [5, 6], including adding folate in the COC, because it is known that folate is involved in metabolic processes through nucleotide synthesis, DNA replication, which ensure cell division and growth [7, 8], the level of complication in the use of contraception remains significant and not fully studied from the standpoint of its impact on the functional state of FPS. Therefore, it is of interest to study the peculiarities of its functioning in women who used different methods of contraception before pregnancy.

The aim – to reduce the incidence of perinatal pathology in women who have used various methods of contraception, based on the study of the functional state of FPS, as well as improving diagnostic measures and tactics of pregnancy management.

2. Materials and methods

The study was conducted from 2017 to 2019 on the basis of the Department of Obstetrics, Gynecology and Perinatology on the basis of the Kyiv Maternity Hospital No. 1, as well as Brovary Multidisciplinary Clinical Hospital. For the purpose of the study, 140 pregnant women were selected and, depending on one or another method of contraception in the anamnesis, they were divided between groups and a control group was formed: Group I, or control – 35 women who did not use contraceptives before pregnancy; Group II – 35 women who had a history of COC use; Group III – 35 women who took COC + F; Group IV – 35 women who used IUC.

The average age of the studied pregnant women in the intergroup comparison did not differ significantly. In the context of employment in all groups, working women predominated: from 74.3 % in the control group to 85.7 % in group III. The vast majority of pregnant women in each group had higher education (from 74.3 % in group IV to 91.4 % in group III) and had a registered marriage, namely: 85.7 % in the control and IV groups, 91.4 % in the II and III ones. The age of onset of sexual life of the studied women also did not differ significantly, and most of them had no more than two sexual partners and were multipara. Young first-time-mothers were not included in the sample. The study involved women without severe ingenious and extragenital pathologies.

Assessment of FPS function and fetal status was performed on the basis of clinical, laboratory and instrumental studies during pregnancy and childbirth [9; 10]. Particular attention was paid to the additional inclusion in the diagnostic measures and tactics of pregnancy assessment of folic acid levels at 6–8 weeks and determination of the most informative endocrinological parameters (human chorionic gonadotropin (hCG), progesterone (P4), free estriol (uE3) and placental lactogen PL) with their different combination depending on the gestational age (6–8, 18–22, 30–32 and 37–40 weeks of pregnancy). A pathomorphological examination of the placenta of women in labor with the determination of fetal/placental ratio (F/PR) in the postpartum period was also performed.

The study was conducted in accordance with the Declaration of Helsinki according to the conclusion of the Commission on Ethics of the National Medical Academy of Postgraduate Education named after P.L. Shupyk (protocol No. 2 dated January 10, 2017). Informed consent to participate in the study was obtained from all women.

Statistical processing of the obtained data was performed using Statistica and Microsoft Office Excel. Evaluation of the statistical significance of the obtained data was performed using the Newman-Kayles and χ^2 criteria. The differences were considered significant at $p < 0.05$.

3. Results

The study of pregnancy revealed some differences in the functional state of FPS depending on the method of contraception in the anamnesis. Thus, the analysis of the first half of pregnancy showed that in group III, in which women used COC+F, women with threatened abortion were absent, which is significantly lower than in the control, II and IV groups, while IUC in the history resulted in more women with not only threatened abortion but also bacterial vaginosis (BV) compared to other groups (**Table 1**).

Table 1

Peculiarities of pregnancy in the studied women

Indicators	Groups of women				The level of significance (p)
	Control group n=35	Group II n=35	Group III n=35	Group IV n=35	
	% (abs.)	% (abs.)	% (abs.)	% (abs.)	
The first half of pregnancy					
Threatened abortion	11.4 (4)	11.4 (4)	–	31.4 (11)	p _{II-K} >0.05; p _{III-K} <0.05; p _{IV-K} <0.05; p _{II-III} <0.05; p _{II-IV} <0.05; p _{III-IV} <0.01
Bacterial vaginosis	–	2.9 (1)	2.9 (1)	17.1 (6)	p _{II-K} >0.05; p _{III-K} >0.05; p _{IV-K} <0.01; p _{II-III} >0.05; p _{II-IV} <0.05; p _{III-IV} <0.05
The second half of pregnancy					
Threat of premature birth	8.6 (3)	5.7 (2)	5.7 (2)	28.6 (10)	p _{II-K} >0.05; p _{III-K} >0.05; p _{IV-K} <0.05; p _{II-III} >0.05; p _{II-IV} <0.05; p _{III-IV} <0.05
Low-lying placenta	2.9 (1)	2.9 (1)	–	17.1 (6)	p _{II-K} >0.05; p _{III-K} >0.05; p _{IV-K} <0.05; p _{II-III} >0.05; p _{II-IV} <0.05; p _{III-IV} <0.01
Placental dysfunction	17.1 (6)	17.1 (6)	2.9 (1)	40 (14)	p _{II-K} >0.05; p _{III-K} <0.05; p _{IV-K} <0.05; p _{II-III} <0.05; p _{II-IV} <0.05; p _{III-IV} <0.01
Fetal growth restriction	2.9 (1)	2.9 (1)	–	17.1 (6)	p _{II-K} >0.05; p _{III-K} >0.05; p _{IV-K} <0.05; p _{II-III} >0.05; p _{II-IV} <0.05; p _{III-IV} <0.01

The second half of pregnancy was also accompanied in some pregnant women by the corresponding complications, among which most often, as can be seen from table 1, there was placental dysfunction and the threat of premature birth. The results showed that taking in anamnesis COC and COC+F is quite positive for a normal pregnancy, in contrast to the IUC. However, given the number of women with PD, the use of COC+F was significantly better compared not only with the use of IUC, but also with COC.

In addition, the course of pregnancy was marked by the occurrence of other complications, including early toxemia, fetal distress, mild anemia, cervical insufficiency (CI), placental abruption, polyhydramnios and dehydration. However, their frequency was low and the differences between the groups were insignificant.

The clinical course of childbirth was characterized by premature rupture of membranes (PROM) (control group – 2.9 % (i. e. in one woman), II – 0 % (there were no cases), III – 2.9 % (in one woman), IV – 17.1 % (in six women); $p_{II-C} > 0.05$, $p_{III-C} > 0.05$, $p_{IV-C} < 0.05$, $p_{II-III} > 0.05$, $p_{II-IV} < 0.01$, $p_{III-IV} < 0.05$), anomalies of labor (control group – 2.9 % (in one woman), II – 2.9 % (in one woman), III – 2.9 % (in one woman), IV – 17.1 % (in six women); $p_{II-C} > 0.05$, $p_{III-C} > 0.05$, $p_{IV-C} < 0.05$, $p_{II-III} > 0.05$, $p_{II-IV} < 0.05$, $p_{III-IV} < 0.05$), fetal distress during childbirth (control group – 2.9 % (in one woman), II –

2.9 % (in one woman), III – 0 % (there were no cases), IV – 11.4 % (in four women); $p_{III-IV} < 0.05$). The significance of the differences between IV and other groups indicates a less favorable effect of the use of IUC in the anamnesis, in contrast to the use of COC, COC+F and the general non-use of any of these methods of contraception.

After birth, almost all newborns had a satisfactory condition: at the level of 100 % (i. e. 35 newborns) in group III, 97.1 % (34 newborns) in the control and II groups, as well as 82.9 % (29 newborns) in group IV, which is significantly lower than these indicators ($p_{II-C} > 0.05$; $p_{III-C} > 0.05$; $p_{IV-C} < 0.05$; $p_{II-III} > 0.05$; $p_{II-IV} < 0.05$; $p_{III-IV} < 0.01$). In addition, in the group in which pregnant women used IUC, 14.3 % (i.e., five newborns) had mild asphyxia, and 2.9 % (one newborn) had moderate asphyxia.

In the process of deeper study of the functional state of FPS, the following results were obtained. During 6–8 weeks of pregnancy, the average level of folic acid saturation was highest in group III and was 16.1 ± 1.8 ng/ml, which differed significantly from that in the control group, in which it was at the level of 9.5 ± 0.9 ng/ml, in group II – 9.2 ± 1.3 ng/ml and in group IV – 9.4 ± 1.2 ng/ml ($p_{II-C} > 0.05$; $p_{III-C} < 0.01$; $p_{IV-C} > 0.05$; $p_{I-III} < 0.01$; $p_{II-IV} > 0.05$; $p_{III-IV} < 0.01$). HcG was characterized by statistically significantly higher in group III (164992.4 ± 5896.3 mIU/ml) and significantly lower in group IV (116568.8 ± 11538.8 mIU/ml) average levels, compared with the control group – 141017 ± 5440.3 mIU/ml – and group II – 139758.6 ± 5566.1 mIU/ml ($p_{II-C} > 0.05$; $p_{III-C} < 0.01$; $p_{IV-C} < 0.01$; $p_{II-III} < 0.01$; $p_{II-IV} < 0.01$; $p_{III-IV} < 0.01$). A similar picture developed with respect to P4: significantly the highest average level in group III (69.9 ± 4.5 ng/ml), and the lowest – in group IV (42.5 ± 4.1 ng/ml) ($p_{II-C} > 0.05$; $p_{III-C} < 0.01$; $p_{IV-C} < 0.01$; $p_{II-III} < 0.01$; $p_{II-IV} < 0.01$; $p_{III-IV} < 0.01$).

The study of endocrinological parameters at 18–22 weeks of pregnancy, namely hCG, P4, uE3 and PL as characteristic of this gestational age, revealed the following trends. The maximum mean value of hCG was in group III (37074.3 ± 3182.4 mIU/ml), and the minimum – in group IV (30467.9 ± 2054.6 mIU/ml), with statistical significance ($p < 0.05$) differences between IV and other groups. The highest mean P4 was recorded in group III (82.7 ± 2.4 ng/ml), and the lowest – in group IV (69.7 ± 3.9 ng/ml) ($p_{II-C} > 0.05$; $p_{III-C} < 0.05$; $p_{IV-C} < 0.05$; $p_{II-III} < 0.05$; $p_{II-IV} < 0.05$; $p_{III-IV} < 0.01$). The average values of uE3 were in the control group at the level of 5.4 ± 0.5 ng/ml, in II – 5.1 ± 0.4 ng/ml, in III – 5.7 ± 0.3 ng/ml, in IV group – 4.5 ± 0.4 ng/ml (significantly the lowest rate) ($p_{II-C} > 0.05$; $p_{III-C} > 0.05$; $p_{IV-C} < 0.01$; $p_{II-III} > 0.05$; $p_{II-IV} < 0.05$; $p_{III-IV} < 0.01$).

The maximum mean value of PL occurred in group IV (4.7 ± 0.5 mg/L), in particular because there was an excess of the norm in 17.1 % of pregnant women, i.e. in six women in this group, at 2.9 % (one) of pregnant women with this disorder in group II ($p_{II-C} > 0.05$; $p_{III-C} > 0.05$; $p_{IV-C} < 0.01$; $p_{II-III} > 0.05$; $p_{II-IV} < 0.05$; $p_{III-IV} < 0.01$). The minimum mean value of PL was in the control (3.5 ± 0.2 mg/L), while in group II the index was on average at 3.8 ± 0.3 mg/L, and in group III – at level 3.6 ± 0.1 mg/L, with significant differences between IV and other groups ($p_{II-C} > 0.05$; $p_{III-C} > 0.05$; $p_{IV-C} < 0.05$; $p_{II-III} > 0.05$; $p_{II-IV} < 0.05$; $p_{III-IV} < 0.05$).

The use of ultrasound examination (UE) at 18–22 weeks of pregnancy made it possible to clinically detect in group IV a significantly higher frequency of FPS dysfunction, such as: premature maturation of the placenta and Low-lying placenta. There was also marginal placenta previa and placental hyperplasia, but their frequency was low and the differences between the groups were insignificant.

During 30–32 weeks of pregnancy, the average values of these endocrinological parameters had a similar trend. HcG in group III was significantly the highest (33977.6 ± 1300.8 mIU/ml), and in IV – the lowest (30143.4 ± 1489.3 mIU/ml); $p_{II-C} > 0.05$; $p_{III-C} < 0.05$; $p_{IV-C} > 0.05$; $p_{II-III} < 0.01$; $p_{II-IV} > 0.05$; $p_{III-IV} < 0.01$). The use of COC+F led to an increase in the mean value of P4, then the IUC – to a certain decrease ($p_{II-C} > 0.05$; $p_{III-C} < 0.01$; $p_{IV-C} < 0.05$; $p_{II-III} < 0.01$; $p_{II-IV} < 0.05$; $p_{III-IV} < 0.01$). Regarding uE3, in group IV there was a decrease in its average value, compared with other groups ($p_{II-C} > 0.05$; $p_{III-C} > 0.05$; $p_{IV-C} < 0.01$; $p_{II-III} > 0.05$; $p_{II-IV} < 0.01$; $p_{III-IV} < 0.01$).

Regarding PL, it should be noted that its average values in the analyzed groups did not differ significantly, in contrast to the number of pregnant women in whom it was recorded exceeding or decreasing below normal. Thus, in the control group was recorded 8.6 % of pregnant women (i. e. three) with the value of this indicator above normal, in group II – 5.7 % (two) pregnant women

above normal and 2.9 % (one) women below norms; in group III – no deviations from the norm; in group IV – 20 % (seven) of pregnant women above normal and 5.7 % (two) of women below normal, which is statistically significant ($p_{II-C}>0.05$; $p_{III-C}>0.05$; $p_{IV-C}<0.05$; $p_{II-III}>0.05$; $p_{II-IV}<0.05$; $p_{III-IV}<0.01$).

UE at this time of pregnancy showed the highest number of complications in the group with a history of IUC, and the lowest - with COC+F, there were significant differences between IV and other groups regarding premature placental maturation (5.7 % (two)) of pregnant women in the control and II groups, in 2.9 % (in one) women in group III and in 22.9 % (in eight) persons in group IV; $p_{II-C}>0.05$; $p_{III-C}>0.05$; $p_{IV-C}<0.05$; $p_{II-III}>0.05$; $p_{II-IV}<0.05$; $p_{III-IV}<0.05$).

Doppler results showed impaired blood flow in the umbilical artery in 5.7 % (two) of pregnant women from the control, 2.9 % (one) from group II and 8.6 % (three) women from group IV. There were no such violations in group III. Also in all groups there were no disturbances of a blood flow in a middle cerebral artery of a fetus. Cardiotocogram (CTG) and biophysical profile (BP) were within normal limits.

Endocrinological parameters (P4, uE3, PL) at 37–40 weeks showed the best mean values in the group in which women before pregnancy used COC+F (in particular in the part of uE3 significantly higher than the control and a group with a history of COC), and significantly worse results – in the group in which they used IUC, compared with other groups.

At UE in this period of pregnancy the presence of such complications as: placental hyperplasia in the control and II groups – 2.9 % (in one pregnant woman in each group), in III – 0 % (there were no cases), in IV – 6.1 % (in two) and placental hypoplasia (3.0 % (in one) in group IV), polyhydramnios (2.9 % (in one) in group III and 6.1 % (in two) in group IV), dehydration (in control and II groups – 2.9 % (one pregnant woman), in III – 0 % (cases were absent), in IV – 9.1 % (in three), as well as FGR (in control and II groups – 2.9 % (in one pregnant woman in each group), in III – 0 % (there were no cases), in IV – 12.1 % (in four) %; $R_{III-IV}<0.05$). By the time of the examination, one woman in the control group and two in the IV group had premature births.

Doppler showed that the pulsation index (IP) of the umbilical artery at 37–40 weeks of pregnancy was in the control group on average at 0.90 ± 0.07 , in group II – 0.89 ± 0.06 , in group III – 0.87 ± 0.05 , in group IV – 1.01 ± 0.09 ($p_{II-C}>0.05$; $p_{III-C}>0.05$; $p_{IV-C}<0.05$; $p_{II-III}>0.05$; $p_{II-IV}<0.05$; $p_{III-IV}<0.05$); IP of the middle cerebral artery of the fetus – at the level of 1.73 ± 0.01 in the control, 1.72 ± 0.01 in group II, 1.75 ± 0.02 in group III and 1.56 ± 0.03 in group IV ($p_{II-C}>0.05$; $p_{III-C}>0.05$; $p_{IV-C}<0.05$; $p_{II-III}>0.05$; $p_{II-IV}<0.05$; $p_{III-IV}<0.05$).

The gestational age of 37–40 weeks was marked by a CTG score of 8–10 on the Fisher scale in 97.1 % in the control and II groups (i. e. in 33 and 34 pregnant women, respectively), in 100 % (in 35 pregnant women) – in group III and in 81.8 % (in 27 pregnant women) – in group IV ($p_{II-C}>0.05$; $p_{III-C}>0.05$; $p_{IV-C}<0.05$; $p_{II-III}>0.05$; $p_{II-IV}<0.05$; $p_{III-IV}<0.05$). Determination of BP in this period showed in most pregnant women a satisfactory fetal condition (7–10 points): 100 % in the control (i. e. 34 pregnant women), 97.1 % (34 pregnant women) in the II, 100 % in 35 pregnant women) in group III and 87.9 % (in 29 pregnant women) in group IV ($p_{II-C}>0.05$; $p_{III-C}>0.05$; $p_{IV-C}<0.05$; $p_{II-III}>0.05$; $p_{II-IV}>0.05$; $p_{III-IV}<0.05$).

A pathomorphological examination of the placenta of women in labor with the determination of F/PR was also performed. Its mean value was 0.14 ± 0.007 in the control group, 0.15 ± 0.009 in group II, 0.14 ± 0.006 in group III and 0.17 ± 0.011 in group IV (maximum) ($p_{II-C}>0.05$; $p_{III-C}>0.05$; $p_{IV-C}<0.01$; $p_{II-III}>0.05$; $p_{I-IV}<0.01$; $p_{III-IV}<0.01$).

In addition, it was macroscopically determined that in the control, II and III groups, most placentas had a normal structure. Microscopic examination of these groups revealed minor involutive-dystrophic changes in most placentas, compared with placentas of women with FPS disorders, in whom the changes were more pronounced. In patients who were in group IV and who had PD during pregnancy, the placenta was characterized by the most pronounced dystrophic changes.

4. Discussion

The normal state of FPS plays a key role in the normal course of pregnancy and childbirth, as well as in ensuring satisfactory fetal development. Based on the data of modern literature, the

key symptom complex that reflects the deviation from the normal functioning of FPS is PD, which may be accompanied by polyhydramnios, hypohydramnios, FGR, fetal distress, etc. [11, 12]. In addition, during pregnancy, complications such as threatened abortion, early toxicosis, BV, the threat of premature birth, anemia, CI and others may occur [13, 14]. As a result, it can adversely affect the condition of the newborn. Therefore, studying the functioning of FPS in women using different methods of contraception in the anamnesis, the main attention was paid to the relevant disorders that occur in it.

In the process of family planning, one of the key links is contraception, the choice of methods which depends on age, health status, the relationship between partners, and so on. However, according to recent data, the most common, if we do not take into account barriers, are COC and IUC [15, 16]. COC+F has also been gaining popularity recently. This is due to the fact that folic acid deficiency during pregnancy, especially in the first weeks, leads to impaired chorionic cell proliferation and placental formation, which subsequently manifests itself in the occurrence of PD and FGR, as well as increases the likelihood of miscarriage, including the threat of premature birth [17, 18].

In this context, the results of the study confirmed the advantage of using a method of contraception such as COC+F, compared with the use of IUC, and in some respects – and take of COC.

Also one of the common factors of PD is inflammatory processes of the pelvic organs. In turn, the literature data indicate the frequent cause of such inflammatory processes using IUC [19, 20]. The results obtained by us are consistent with the following data.

Thus, the study made it possible to identify new aspects of the pathogenesis of disorders of the functional state of FPS, as well as to determine the most optimal method of contraception and one that acts as a risk factor for these disorders.

Study limitations. The study did not include women with severe genital and extragenital pathologies, young first-time-mothers, and women who refused to participate in the study.

Prospects for further research. Study of the features of folate metabolism in women who have used various methods of contraception, in order to increase the effectiveness of pre-pregnancy training of such women in terms of correction of folic acid levels.

5. Conclusions

The results obtained during the study provided an opportunity to identify new aspects of the pathogenesis of functional disorders of FPS, which take into account the use in the history of various methods of contraception. In particular, a decrease in folic acid levels in pregnant women below normal at 6–8 weeks is accompanied by the subsequent occurrence of threatened abortion and the development of PD. In addition, placental hormonal dysfunction, namely hcG, P4, uE3, and PL synthesis, that occurs at different stages of gestation, especially in women with a history of IUC, is a preclinical manifestation of PD and related complications.

Also, a study of the clinical course of pregnancy and childbirth showed that women with a history of IUC, compared with COC and COC+F, had a higher incidence of complications and fewer newborns with a satisfactory condition at birth (82.9 % vs. 97.1 % and 100 % respectively).

This made it possible to determine the presence of a history of IUC as a risk factor for functional disorders of FPS, namely the occurrence of PD, as confirmed by pathomorphological studies, and the use of a history of COC+F is the best option for women of different risk groups. complications and prevent functional disorders of FPS.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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