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Dopplerometry of fetoplancentral blood flow in the dynamics of pregnancy in women with treated infertility caused by hyperprolactinemia syndrome of tumocular and non-tumocular genesis

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Abstract

The aim of the study was to study the state of blood circulation in the fetoplacental system in the dynamics of gestation using Dopplerometry in women with cured infertility due to hyperprolactinemia syndrome of tumor and non-tumor genesis. **Material and methods.** 57 pregnant women with cured infertility due to hyperprolactinemia syndrome (21 women with pituitary microprolactinomas and 36 patients with idiopathic hyperprolactinemia), 30 relatively healthy pregnant women of the control group without neuroendocrine disorders were under observation. Doppler study of the pulsatile index (PI) of blood flow in the uterine arteries at 11-12, 29-31 and 36-37 weeks, PI of the umbilical artery, middle cerebral artery and ductus venosus at 29-31 and 36-37 weeks was performed. Cerebroplacental ratio was assessed to assess the distribution of blood flow between the brain and the placenta of the

fetus. **Results.** The average PI of the uterine arteries was the highest at 11-12 weeks of gestation and throughout pregnancy exceeded the similar indicator in pregnant women without neuroendocrine disorders, but was not statistically different in individuals with hyperprolactinemia of tumor and non-tumor genesis. The average PI of the umbilical artery exceeded the similar indicator in healthy pregnant women in the second and third trimesters, and at 36-37 weeks it was significantly higher in women with microprolactinomas compared with individuals with idiopathic hyperprolactinemia. The average PI of the middle cerebral arteries in the second and third trimesters was lower than that in pregnant women without neuroendocrine disorders, but there were no significant statistical differences between pregnant women with hyperprolactinemia of tumor and non-tumor genesis. Cerebroplacental ratio was reduced in individuals with hyperprolactinemia of tumor and non-tumor genesis compared to pregnant women without neuroendocrine disorders, while among pregnant women with hyperprolactinemia in the cohort of individuals with microadenomas this indicator was lower than in pregnant women without neuroendocrine disorders. No differences were found in the average PI of the ductus venosus in pregnant women with hyperprolactinemia and pregnant women without neuroendocrine disorders. **Conclusions.** Pregnancy in women with cured infertility due to hyperprolactinemia syndrome of tumor and non-tumor genesis is characterized by abnormal changes in blood circulation in the fetoplacental system in the dynamics of gestation, which indicate the presence of fetoplacental dysfunction of varying degrees of severity in such women and the need for appropriate therapeutic and preventive measures during pregnancy.

Keywords: hyperprolactinemia syndrome; macroprolactinoma; idiopathic hyperprolactinemia; pregnancy; fetoplacental blood flow; Dopplerometry; uterine arteries; umbilical artery; middle cerebral arteries; ductus venosus; fetoplacental dysfunction.

Hyperprolactinemia is the most common disorder of the hypothalamic-pituitary axis [1, 2]. Hyperprolactinemia occurs in less than 1% of the general population and in 5–14% of patients with secondary amenorrhea. The most common type is a prolactin (PRL)-secreting tumor – prolactinoma, which accounts for up to 40% of all clinically detected pituitary adenomas [3]. Hyperprolactinemia syndrome is a symptom complex observed against the background of elevated PRL levels, the most characteristic manifestation of which is a violation of the function of the reproductive system, and in severe cases, in the presence of

prolactin-secreting pituitary tumors, it is accompanied by neurological and neuroophthalmological disorders [4]. Hyperprolactinemia syndrome is one of the most common etiologies of infertility in women. Excessive PRL secretion reduces pulsatile GnRH release and disrupts normal gonadal steroid secretion, leading to positive feedback at the pituitary and hypothalamic levels, and ultimately to infertility [2].

Modern technologies and new drugs allow for the successful treatment of hyperprolactinemia syndrome, including one of its main manifestations - infertility. The use of dopamine agonists is accompanied by a high frequency of pregnancy in patients with hyperprolactinemia syndrome, but the literature on this issue is extremely limited. This indicates the relevance of the problem of studying the course of the gestational process and childbirth in patients with hyperprolactinemia syndrome. According to researchers, the presence of hyperprolactinemia in pregnant women leads to an increase in the frequency of complications of gestation, childbirth, and the postpartum period [5]. Numerous studies associate elevated PRL levels in maternal serum, amniotic fluid, or cervicovaginal secretions with pregnancy loss and/or premature birth [6-11]. It has now been established that almost all pregnancy complications, such as preeclampsia, fetal growth restriction syndrome, and threatened abortion, are accompanied by fetoplacental dysfunction, a pathological phenomenon that leads to premature birth and is the leading cause of perinatal morbidity and mortality worldwide [12].

Fetoplacental dysfunction consists of a complex of disorders of the trophic, endocrine and metabolic functions of the placenta, leading to its inability to maintain adequate and sufficient exchange between the mother and fetus. The placenta is a vascular organ. Hormones affect angiogenesis either directly through their action on endothelial cells or indirectly by regulating proangiogenic factors such as vascular endothelial growth factor. Importantly, the local microenvironment of endothelial cells can determine the outcome of the action of hormones on angiogenesis. Members of the growth hormone/prolactin/placental lactogen, renin-angiotensin and kallikrein-kinin systems, which have a stimulating effect on angiogenesis, can acquire antiangiogenic properties after proteolytic cleavage [13]. It is reasonable to assume that abnormalities in the metabolism of lactogenic hormones during pregnancy will contribute to the development of fetoplacental dysfunction.

One of the methods for assessing the functioning of the “mother-placenta-fetus” system during gestation is Dopplerometry of fetoplacental blood flow. The method has been used for more than thirty years and is characterized by simplicity and high informativeness.

The high resolution of Dopplerometry allows you to visualize and identify the smallest vessels of the microcirculatory bed [14].

Assessment of the state of blood flow of the fetoplacental system during pregnancy in women with cured infertility due to hyperprolactinemia of tumor and non-tumor genesis is an urgent task of modern obstetrics.

The aim of the study was to study the state of blood circulation in the fetoplacental system in the dynamics of gestation using Dopplerometry in women with cured infertility due to hyperprolactinemia syndrome of tumor and non-tumor genesis.

Material and methods

The work was carried out at the Odessa National Medical University (ONMedU) from 2021 to 2024 within the framework of the research topic "Improving the method of prevention, diagnosis and treatment of diseases of the female reproductive system using the latest medical technologies" (state registration number 0117U007494), approved by the Bioethics Commission of ONMedU on November 8, 2021, protocol number 2/21. The clinical bases of the study were LLC "Clinic of Reproductive Medicine "Nadiya Odesa"" of Odessa, LLC "AIRMED Specialized Hospital" of Odessa, Center for Perinatal Care of the Municipal Clinical Hospital No. 10 of the Odessa City Council. Informed consent was obtained from all women.

57 pregnant women of group P with cured infertility due to hyperprolactinemia syndrome and 30 conditionally healthy pregnant women of control group K without neuroendocrine disorders were under observation. Pregnant women with macroprolactinomas, PCOS and thyroid dysfunction were not included in the study. In group P, 21 women of group PA had pituitary microprolactinomas, 36 patients of group PG were treated at the pregravid stage for hyperprolactinemia syndrome of non-neoplastic genesis.

To determine the status of the fetoplacental system during pregnancy, Doppler studies of the pulsatile index (PI) of uterine artery blood flow were performed at 11-12, 29-31 and 36-37 weeks, and PI of the umbilical artery, middle cerebral artery and ductus venosus at 29-31 and 36-37 weeks. Cerebroplacental ratio was assessed to assess the distribution of blood flow between the brain and placenta in response to potential oxygen deficiency. It was calculated by the ratio of PI (blood flow resistance index) in the fetal middle cerebral artery to PI in the umbilical artery [14].

Ultrasound scans and measurements, Dopplerography were performed by expert-class ultrasound operators with extensive experience in obstetric ultrasound and a certificate of

competence granted by The Fetal Medicine Foundation (FMF) on expert-class ultrasound scanners.

Statistical processing of the research materials was carried out using the EXCEL program. The arithmetic mean (M), standard deviation error (±SEM), Student's t-test, and χ^2-test were calculated.

Results and their discussion

The average age of patients in the studied groups at the time of pregnancy did not differ significantly between the groups: in the P group it was (28.16±0.38) years, in the PA group – (27.86±0.67) years, in the PG group – (28.33±0.46) versus (27.50±0.46) years in the K group ($p>0.05$).

The body mass index (BMI) of women with microprolactinomas exceeded the BMI in individuals with idiopathic hyperprolactinemia (in the PA group – (24.18±0.75) kg/m^2 vs. (21.97±0.52) kg/m^2 in the GP group ($p_{pa-pg}<0.02$)). BMI in the control group was (21.71±0.43) kg/m^2 ($p_{pa-k}<0.01$, $p_{pg-k}>0.05$).

The distribution of primary and secondary in the studied groups had no significant differences, primary infertility prevailed in all groups: in the P group - in 44 (77.19%) cases, in the PA group - in 16 (76.19%) in the PG group - in 28 (77.78%).

The age at the time of diagnosis of pituitary microprolactinoma was equal to (23.48±0.65) years in the PA group ($p>0.05$). The maximum diameter of microprolactinomas among the examined patients before the start of treatment varied from 2 to 6 mm and on average in the PA group was (3.58±0.40) mm ($p>0.05$), and the PRL level was (144.90±10.33) ng/ml. Patients with microprolactinomas received treatment with dopamine agonists: 15 (71.43%) patients - with cabergoline and 6 (28.57%) patients - with bromocriptine.

Until conception, patients received bromocriptine therapy at a dose of 2.5-20 mg/day, on average (9.58±1.19) mg/day, and cabergoline was taken at a dose of 0.25 mg/week to 1.0 mg/week, the average dose in the PA group was (0.80±0.06) mg/week.

As a result of dopamine agonist treatment, the smallest diameter of microprolactinoma decreased in the PA group and before pregnancy was on average (3.76±0.24) mm, and the lowest recorded PRL level before pregnancy was (15.81±0.55) ng/ml ($p>0.05$).

The term of normalization of PRL level reached on average in the PA group – (4.15±0.27) months, in the PG group – (2.91±0.30) months ($p_{pa-pg}<0.02$). The menstrual cycle was established on average in the PA group after (4.30±0.22) months, in the PG group – after

(3.25±0.20) months (p_{pa-pg}<0.02). Ovulation resumed on average in the PA group after (6.19±0.25) months, in the PG group – after (4.61±0.20) months (p_{pa-pg}<0.02). Continuous treatment with dopamine agonists in the PA group took on average (7.29±0.31) months, in the PG group – (5.89±0.20) months (p_{pa-pg}<0.03). Pregnancy was achieved on average in the PA group after (8.90±0.34) months, in the PG group – after (7.22±0.33) months (p_{pa-pg} <0.02).

When conducting Dopplerography during pregnancy, the average PI of the uterine arteries in both the control group and the groups of women with hyperprolactinemia was the highest at 11-12 weeks of pregnancy and was equal in the P group (1.25±0.04), in the PA group (1.33±0.07), in the PG group (1.21±0.06) vs (1.02±0.04). The average PI of uterine arteries in the second and third trimesters of gestation in women in group P was more than similar to that in the control, but did not differ between groups with microprolactinomas and hyperprolactinemia of non-neoplastic genesis: at 29-31 weeks of pregnancy in group P it was (0.92±0.02), in group PA (1.05±0.03) and in group PG (0.86±0.03) vs. (0.79±0.02) in group K; at 36-37 weeks in the PA group it was equal to (0.90±0.02), in the PA group (0.94±0.02) and in the PG group (0.88±0.03) vs. (0.69±0.02) in the K group (p_{p-k}<0.01, p_{pa-k}<0.01, p_{pg-k}<0.01, p_{pa-pg}>0.05) (Table 1).

Table 1

The average pulsatile index of uterine arteries in the studied groups during pregnancy, M±SEM

Group	Gestation period, weeks		
	11-12	29-31	36-37
P, n=57	1.25±0.04[k]	0.92±0.02 [k]	0.90±0.02 [k]
PA, n=21	1.33±0.07 [k]	1.05±0.03 [k]	0.94±0.02 [k]
PG, n=36	1.21±0.06 [k]	0.86±0.03 [k]	0.88±0.03 [k]
K, n=30	1.02±0.04	0.79±0.02	0.69±0.02

Notes: 1. [k] – statistically significant difference with the indicator of group K (p<0.05); 2. No statistically significant difference was found between the PA and PG groups (p>0.05).

The umbilical artery PI in the P group at 29-31 weeks was (1.06±0.02), in the PA group (1.08±0.03), PG group (1.06±0.02) vs. (0.95±0.02) in the K group (p_{p-k}<0.01, p_{pa-k}<0.01, p_{pg-k}<0.01, p_{pa-pg}>0.05), at 36-37 weeks of pregnancy – respectively (1.02±0.02), (1.09±0.03), (0.99±0.02) vs. (0.92±0.02) (p_{p-k}<0.01, $p_{pa-k<}$0.01, ppg-k<0.01, p_{pa-pg}<0.04) (Table 2).

The PI of the middle cerebral artery in the P group at 29-31 weeks was (1.74±0.04), in the PA group (1.68±0.04), in the PG group (1.76±0.06) vs. (2.15±0.05) in the K group (p_{p-k}<0.01, p_{pa-k}<0.01, p_{pg-k}<0.01, p_{pa-pg}>0.05), at 36-37 weeks of pregnancy – respectively (1.64±0.04), (1.62±0.04), (1.65±0.06) vs. (1.81±0.04) (p_{p-k}<0.01, p_{pa-k}<0.01, p_{pg-k}<0.01, p_{pa-pg}>0.05) (see Table 2).

Table 2

Pulsation index of the umbilical and middle cerebral arteries, and the fetal ductus venosus in the studied groups of pregnant women during pregnancy, M±SEM

Group	Gestation period, weeks	
	29-31	36-37
Umbilical artery		
P, n=57	1.06±0.02 ^{k}	1.02±0.02 ^{k}
PA, n=21	1.08±0.03 ^{k}	1.09±0.03 $^{k.pg}$
PG, n=36	1.06±0.02 ^{k}	0.99±0.02 $^{k.pa}$
K, n=30	0.95±0.02	0.92±0.02
Middle cerebral artery		
P, n=57	1.74±0.04 ^{k}	1.64±0.04 ^{k}
PA, n=21	1.68±0.04 ^{k}	1.62±0.04 ^{k}
PG, n=36	1.76±0.06 ^{k}	1.65±0.06
K, n=30	2.15±0.05	1.81±0.04
Ductus venosus		
P, n=57	0.67±0.01	0.64±0.02
PA, n=21	0.68±0.02	0.66±0.02
PG, n=36	0.67±0.01	0.63±0.02
K, n=30	0.67±0.01	0.69±0.01

Note. $^{pa, pg, k}$ – statistically significant difference with the PA, PG, K group indicator (p<0,05).

PI of the ductus venosus did not have significant differences with the control during pregnancy: in the P group at 29-31 weeks PI was equal to (0.67±0.01), in the PA group (0.68±0.02), PG (0.67±0.01) vs. (0.67±0.01) in the K group (p_{p-k}<0.01, p_{pa-k}>0.05, p_{pg-k}>0.05,

p_{pa-pg}>0.05), at 36-37 weeks of pregnancy – respectively (0.64±0.01), (0.66±0.02), (0.63±0.02) vs. (0.69±0.01) (p_{p-k}>0.05, p_{pa-k}>0.05, p_{pg-k}>0.05, p_{pa-pg}>0.05) (see Table 2).

The cerebro-placental ratio in the P group at 29-31 weeks reached (1.65±0.04), in the PA group (1.57±0.04), in the PG group (1.69±0.06) vs. (2.30±0.07) in the K group (p_{p-k}<0.01, p_{pa-k}<0.01, p_{pg-k}<0.01, p_{pa-pg}>0.05), at 36-37 weeks of pregnancy – respectively (1.66±0.07), (1.51±0.06), (1.73±0.10) vs. (2.29±0.08) (p_{p-k}<0.01, p_{pa-k}<0.01, p_{pg-k}<0.01, p_{pa-pg}<0.04) (see Table 2, Fig. 1).

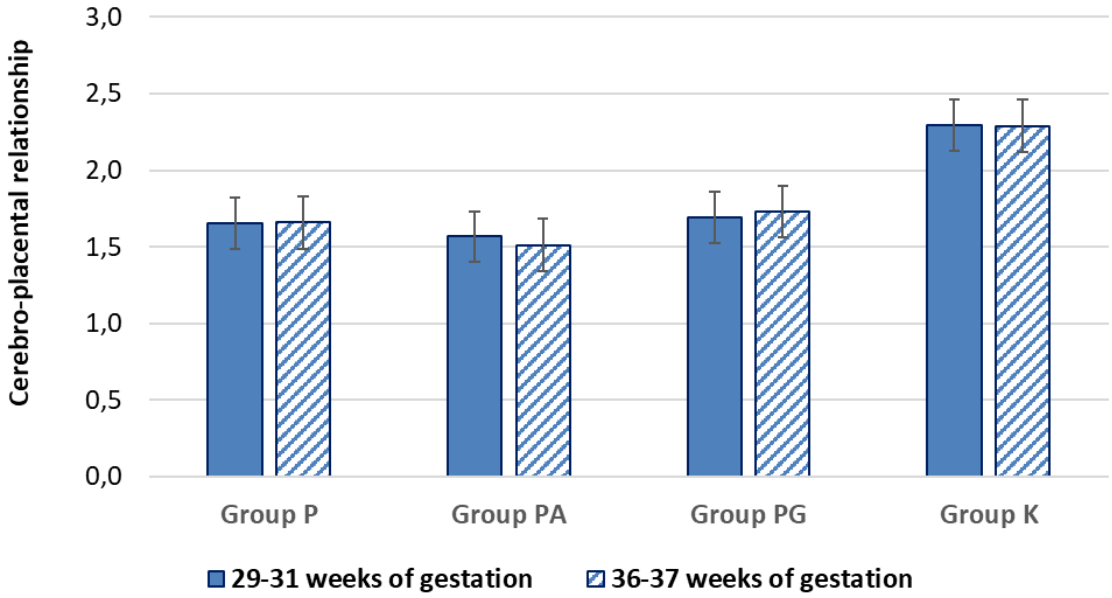

Fig. 1. Cerebro-placental ratio during Doppler measurement of fetoplacental blood flow in the studied groups of pregnant women.

Fetoplacental blood flow increases with the progression of pregnancy. An adequate supply of nutrients and oxygen carried by the fetoplacental blood flow is essential for maternal well-being and fetal growth/development. The change in fetoplacental hemodynamics is achieved primarily through adaptations of the uterine vessels, which include hormonal regulation of myogenic tone, vasoreactivity, release of vasoactive factors, and others, in addition to remodeling of the spiral arteries. Vascular dysfunction leads to increased vascular resistance and decreased blood flow in the fetoplacental circulation [15].

The fetoplacental circulation, which connects the maternal and fetal circulations, is established early in the second trimester [16, 17]. Remodeling of the spiral arteries and functional adaptation of the uteroplacental arteries allow the fetoplacental circulation to become a low-resistance, high-flow system. Adequate fetoplacental blood flow is crucial for

both fetal growth and maternal well-being [18, 19]. Impaired uteroplacental vascular transformation/adaptation has been associated with pregnancy complications [20-22].

Vascular tone is largely determined by intrinsic myogenic regulation, the dynamics of vasoconstrictor and vasodilator effects acting on the vascular system, and flow- or shear-stress-mediated regulation [23]. Pregnancy increases uterine artery myogenic tone in human myometrial arteries [24]. Shear stress, the frictional force on the endothelium in vessels resulting from blood flow, is felt by the endothelium, leading to increased release of vasodilators [25]. In response to shear stress, the acute vascular response in the peripheral circulation is vasodilation [26]. Nitric oxide (NO) is the main mediator of shear stress/flow-induced vasodilation of uterine arteries [27, 28].

Polypeptide hormones and steroid hormones expressed by the placenta or dependent on the placenta for their synthesis are key to stimulating maternal adaptations during pregnancy that support growth in utero. Placentally derived hormones involved in the programming of maternal care include PRL-related hormones and steroid hormones [29].

PRL increases NO production [30] by increasing intracellular calcium [31] and by increasing the expression of carboxypeptidase-D, which releases the nitric oxide synthase (NOS) substrate L-arginine from the C-terminus of polypeptides [32, 33]. PRL has been shown experimentally to induce endothelium-dependent vasodilation via PRL receptors in rat aorta [34]. Recently, it has been shown that the 16-kDa form of PRL, which is cleaved from PRL by cathepsin-D and matrix metalloproteinases, has antiangiogenic effects, whereas full-length PRL has angiogenic effects [35, 36]. Overexpression of 16-kDa impairs cardiac function [22]. It has also been shown that 16-kDa PRL inhibits endothelial NOS activity by modulating intracellular calcium mobilization [37] and by activating protein phosphatase 2A, which leads to dephosphorylation and inactivation of endothelial NOS [38]. Levels of 16-kDa PRL are elevated in plasma, urine, and amniotic fluid obtained from women with preeclampsia [39].

A.S. Chang et al. (2016) [40] found that different degrees of elevated plasma PRL have opposite effects: decreased blood pressure caused by increased NO production when plasma PRL levels are slightly above normal, and increased blood pressure along with cardiac dysfunction caused by decreased NO production when plasma PRL levels are significantly elevated. A threefold increase in plasma PRL levels is sufficient to significantly increase blood pressure and markedly impair cardiac function, with effects mediated by eNOS-produced NO. These data, together with the known association of elevated PRL levels with

preeclampsia, suggest that pregnant women with high PRL levels may require special attention [40]. The basis for placenta-associated pregnancy diseases is fetoplacental dysfunction. Currently, diagnostic criteria for placental dysfunction are lacking, as there are no generally accepted standardized diagnostic methods. Part of the problem is related to the wide variety of terminology used to describe what is known as placental dysfunction [41]. However, with advances in technology, Doppler ultrasound has proven useful in assessing fetal and placental circulation in both healthy and diseased conditions. Four Doppler modalities are fundamental in providing useful information about fetal and maternal circulation, including examination of the umbilical artery, uterine arteries, middle cerebral artery, and ductus venosus [19].

Before the onset of pregnancy, the uterine arteries exhibit low diastolic blood flow, high resistance, and elastic recoil, which is seen in early diastolic notches. Successful placentation involves the removal of the intimal muscle from the vasculature, resulting in blood vessels with vigorous diastolic blood flow, minimal resistance, and no elastic properties. When placentation is successful, Doppler ultrasound demonstrates that remodeling occurs rapidly, such that the notch is lost by 12 weeks of gestation. Resistance is low until 20 weeks of gestation or earlier. When placentation is unsuccessful, the notch persists and resistance remains high, which correlates with fetal complications related to maternal hypertension, including intrauterine growth retardation, preeclampsia, and fetal death [19]. In a study, it was shown that women with cured infertility on the background of hyperprolactinemia of neoplastic and non-neoplastic genesis have an increased mean PI of the uterine arteries throughout pregnancy compared with pregnant women without neuroendocrine disorders, but it is not statistically different in individuals with hyperprolactinemia of neoplastic and non-neoplastic genesis. With increasing placental resistance, Doppler studies of the umbilical artery may demonstrate normal, reduced, absent, or reversed end-diastolic velocity [18, 22]. High placental resistance in early pregnancy is a normal phenomenon. Therefore, it can be expected that end-diastolic velocity will be absent on Doppler studies until 12-14 weeks of gestation. When the placenta successfully sprouts, resistance falls, and Doppler studies of the umbilical artery should demonstrate continuous blood flow until 14-18 weeks of gestation [19]. Persistent umbilical artery resistance throughout pregnancy indicates an increased risk of placental dysfunction, which we found in our study in pregnant women with cured infertility on the background of hyperprolactinemia,

and at 36-37 weeks the average umbilical artery PI was significantly higher in women with microprolactinomas compared to those with idiopathic hyperprolactinemia.

Although umbilical artery Doppler studies provide important information about possible placental dysfunction, a valuable adjunct is the use of middle cerebral artery Doppler studies. Middle cerebral artery blood flow provides information about systemic circulatory responses in the developing fetus and reflects the resistance to flow in the cerebral microcirculation. Normal middle uterine artery Doppler values demonstrate high resistance throughout pregnancy; however, placental disease can be identified by increased diastolic blood flow and decreased PI [19]. In a study, the mean PI of the middle cerebral artery in the second and third trimesters was found to be lower than that in pregnant women without neuroendocrine disorders, with no statistically significant differences between pregnant women with neoplastic and non-neoplastic hyperprolactinemia.

Another form of Doppler imaging that provides insight into placental and fetal health is venous Doppler, which provides cardiac information when the fetal circulation is stressed. The venous waveform that has been shown to provide the best clinical information is the ductus venosus. The use of the ductus venosus has many advantages over other venous waveforms, including its responsiveness to changes in oxygenation, its role as a major regulator of venous return in both abnormal and normal fetal circulation, its independence from cardiac function, its direct view of retrograde right atrial pulse waves, and its ability to visualize retrograde right atrial pulse waves, and its ability to visualize color Doppler signals from as early as 12 weeks of gestation to 40 weeks of gestation [19]. In this study, no differences were found in the mean PI of the ductus venosus between pregnant women with hyperprolactinemia and those without neuroendocrine disorders.

Conclusions

Pregnancy in women with cured infertility due to hyperprolactinemia syndrome of tumoral and non-tumor genesis is characterized by abnormal changes in blood circulation in the fetoplacental system in the dynamics of gestation, which indicate the presence of fetoplacental dysfunction of varying degrees of severity in such women and the need for appropriate therapeutic and preventive measures during pregnancy.

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Contribution of the authors

Nosenko Olena - conceptualization (AAA), methodology (BBBB); formal analysis (SCC).

Martynovska Olha - data collection (EEE, BBB); writing an article (SCC, DDD): statistical processing of materials (AAA, BBB, SSS). All authors have read and approved the published version of the manuscript.

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Conclusion of the commission on bioethics A positive decision of the bioethics commission was received for conducting the research Odessa National Medical University (protocol No. 2/21 dated November 8, 2021), the main moral and ethical principles of the Helsinki Declaration of the World Medical Association for Biomedical Research are observed.

Statement of informed consent

Written informed consent for processing was obtained from the patient(s). personal data and their further use.

Statement on data availability

All information is publicly available, data on a specific patient can be obtained on request from the lead author.

Conflict of interest

The authors declare no conflict of interest