INTRODUCTION
Perinatal period is crucial for the formation of further health of an individual. Though the modern taxonomy of diseases in obstetrics is based on clinical symptoms of mother and not on the pathophysiological mechanisms that are in charge of clinical manifestation. For example, the term “preterm labour” is not indicating what is the cause - infection, disorders of placental blood flow, over distension of uterus, disorders of allogenic recognition, stress of other pathological processes. The same refers to preeclampsia, fetal growth restriction, antenatal fetal death, nausea and vomiting of pregnant, disorders of uterine contractile activity, so the manifestations, when the diagnosis just indicates the clinical symptoms without clarifying specific etiology.

Lack of understanding of these states leads to management of symptoms without treatment of mechanisms that caused the disease, this, in turn, leads to expectation that one diagnostic test or treatment may indicate or cure the other mentioned states. Oxford medical dictionary defines that syndrome is a group of symptoms which consistently occur together, or a condition characterized by a set of associated symptoms. The main in this definition is that a syndrome may be caused by more than one mechanism, or disease or etiology.

Obstetrical complications that cause perinatal morbidity and mortality are syndromes, though they may be named “Great Obstetrical Syndromes” (GOS). This term was widely implemented to clinical practice after 2009, due to publications of G. C. Di Renzo and R. Romero.

THE AIM
The aim to analyze the up to date data concerning prognostication of Great obstetrical syndromes.

MATERIALS AND METHODS
Used database Pubmed from 2004 up till 2019 to search clinical studies of great obstetrical syndromes.

REVIEW AND DISCUSSION
GOS – is a name for a group of gestational complications that occur in approximately 15% of pregnancies. They may cause severe gestational period complications and lead to fetal and maternal mortality, so these syndromes require extraordinary attention, constant monitoring and treatment. The main characteristics of these syndromes are: [1,2]: multiple etiology; a long preclinical period; frequent fetal involvement; adaptive in nature.

The development of these syndromes is a result of complicated relationships between maternal and fetal genomes and the environment. The GOS include [1,2]: preterm labour, premature rupture of membranes, preeclampsia, intrauterine growth restriction, macrosomy, missed pregnancy, antenatal fetal death, spontaneous abortions, placental abruption. Recent publications indicate gestational diabetes (GD) as one of the GOS [3].

GOS are characterized by generalized inflammation, endothelial dysfunction, increased trombine production, the prevalence of antiangiogenic factors that commonly lead to multiple organs and systems damage [4].
According to results of investigations, the main cause of GOS is pathology of deep placentation. Also, one of pathophysiological links in GOS development is dysfunction of haemostasis system.

**RISK FACTORS**
The risk factors of GOS development include anemia, endometriosis, polycystic ovarian syndrome, teenage age, chronic arterial hypertension, previous pregnancy complications by preeclampsia and preterm labour [5].

The recommendations of National Institute for Health and Clinical Excellence (NICE) include routine screening of specific preeclampsia risk factors (primipara, elderly age, increased body mass index (BMI), preeclampsia in family history, chronic renal disease of chronic hypertension, multiple pregnancy, a long interval between pregnancies more than 10 years and preeclampsia in previous pregnancy). The estimated incidence of preeclampsia is from 3% in case of one risk factor up till 30% in case of combination of several risk factors mentioned above [6–9]. According to GOS study in nulliparous women, BMI is the most discriminant maternal characteristic for the prediction of preeclampsia. Maternal characteristics should not be used alone to identify nulliparous women at high risk of preeclampsia [10].

Canadian scientists concluded that the presence in primipara risk factors like age, ethnicity and history allows to determine 55% of women with early preeclampsia risk with specificity 90%. In case of additional usage of biomarkers of blood serum the rate of determination was increased to 75%. Taking into account the fact, that a number of medical centers offer determination of pregnancy-associated plasma protein–A (PAPP–A) in blood serum in the first trimester of pregnancy, at least 50% of all preeclampsia cases may be predicted and probably more than two thirds of severe cases with the rate of false-positive results less than 10%. The value of determination of additional markers of first or early second trimester preeclampsia such as placental growth factor, ingibin, endogline, soluble fmf-like tyrosinkinase - 1 (sFlt–1) are being studied. Though, the answer to this question may be given only after the confirmation of action and benefits of these factors usage in large cohort studies and studies of cost-effectiveness ratio [11–15].

Yu et al. have offered ultrasound screening of first trimester in order to accurately determine the vascular pathology of placenta and for detection of women with increased risk of dangerous obstetrical complications [16]. The investigations proved that women with increased vascular resistance in uterine arteries have a 5 fold time's increased risk of preeclampsia, intrauterine growth restriction or antenatal death development compared to other pregnant. It is assumed, that the possible factors of pathological placentation development are increased cell death and decreased expression of insulin-like growth factor-2 [17].

**PROGNOSTICATION**
One of the glycoproteins which is synthesized by placenta and may have a prognostication value is PAPP-A. It is well known about the use of this marker for screening programs in the first trimester in order to diagnose aneuploidies. Nowadays it is studied as a marker of GOS [18,19].

Furthermore, it was concluded that Dopplerometry of uterine arteries during pregnancy combined with determination of PAPP–A is connected to disorders of trophoblast development [20, 21] and is observed in case of small for gestational age fetuses, intrauterine growth retardation and antenatal fetal death [22–24]. These investigations resulted in a confirmation of coherence between Dopplerometry of uterine arteries and levels of PAPP–A with small for gestational age fetuses and decreased fetal movements in case of an at term pregnancy. Pregnancies complicated by decreased fetal movements and/or small for gestational age fetuses were accompanied by decreased levels of PAPP–A and increased indexes in the uterine arteries in 11–13 weeks of gestation compared to uncomplicated pregnancies. Also, compared to cohort the frequency of small for gestational age fetuses was significantly higher among women with decrease fetal movements in case of an at term pregnancy. Even taking into account such variables as maternal age, BMI, ethnicity, smoking, logistical regress showed independent relationship between levels of PAPP-A, uterine arteries Dopplerometry indexes, small for gestational age fetuses and decrease fetal movements in case of at term pregnancy [25].

It was established that a combined estimation of placental growth factor (PIGF), PAPP-A and a heperglycosalated chorionic gonadotropin (hCG-h) to chorionic gonadotropin (hCG) ratio together with mean arterial pressure in primipara gave the opportunity to receive a test, where the prognostication value AUC was 0.870 for early manifestation of preeclampsia [26]. Though, a self assessment in the second trimester did not have a prognostication value [27].

European Society of Cardiology indicates, that Dopplerometry of uterine arteries after 20 weeks of gestation gives the opportunity to identify women with high risk of gestational hypertension, preeclampsia and intrauterine growth retardation. They also notice, that the rate ratio in patients with doubtful diagnosis indicates a low risk of preeclampsia development [28].

Also worth noting, that there are a number of investigations concerning the function of endoglin in the development of a cascade of pathological processes in case of preeclampsia [29]. Nowadays it is mostly used for evaluation of effectiveness of proton pump inhibitors for preeclampsia treatment on the stage of preclinical, double blind, randomized, placebo-controlled investigations [30] that is one of the new research areas [31, 32].

Another biomarker, the role of which in preeclampsia pathogenesis is widely discussed is vascular endothelial growth factor. It is worth noticing, that it is one of the proteins, which is also in charge of the balance of angiogenic/antiangiogenic signals during placentation [33]. Though, the amount of relevant publications concerning perspectives of the usage of this parameter is minimal [34]. The proof of absence of adequate investigations of its prognostic value is “ignoring the biomarker” by most
of recommendations of leading profile organizations [35]. Nevertheless, in one of recent publications there are data about a new predicting factor of preeclampsia – the ratio between pigment epithelium–derived factor (PEDF) and vascular endothelial growth factor [36].

One of the methods of GOS prognostication is a measurement of mean arterial pressure (MAP) in the first trimester. Recent investigations showed, that among 4700 pregnant women gestational hypertension was diagnosed in 250 (5.3%), preeclampsia - in 241 (5.1%), including preterm in 33 (0.7%) and early in 10 (0.2%) of women. Increased MAP in the first trimester was associated with increased incidence of gestational hypertension (OR 0.77; 95% CI: 0.74–0.80), preterm preeclampsia (0.80; 95% CI: 0.73–0.87), early (0.79; 95% CI: 0.62–0.96) and at term preeclampsia (0.73; 95% CI: 0.70–0.76). The rates of false-positive results of MAP measurement in the first trimester was 10% with the prognostication rates of 39% for gestational hypertension, 34% for at term preeclampsia, 48% for early preeclampsia. In case of combination with pregnant data, the improvement of predicative parameters was observed till 40%, 37%, 55% and 70% accordingly. Therefore it was proved that MAP in the first trimester is a valuable predictor of gestational hypertension and preeclampsia in primipara women [37].

Recent investigations established an important role in violation of estrogen levels in preeclampsia pathogenesis. During pregnancy, estrogen is produced by mainly placenta, unlike the predecessors of androgens, which are produced by adrenal glands of mother and fetus. These processes lead to increased estrogen levels in blood plasma, compared to levels of non pregnant women. Disorders of estrogen production may play a crucial role in appearance of preeclampsia symptoms, as they are exclusively produced by placenta and contribute to angiogenesis and vasodilatation. Previous investigations of estrogen synthesis in case of preeclampsia showed controversial results, probably due to insufficient specificity of the analyzes. Though by implementing reliable analytical protocols with liquid chromatography/mass-spectrometry or gas chromatography/mass-spectrometry, modern investigations indicate a significant decrease of estrogen levels in case of preeclampsia. Close connection between disorders of estrogen regulation and incidence of preeclampsia may substantiate the use of estrogen levels as a biomarker, and also may establish a potential approach to prophylaxes and treatment of preeclampsia.

Estradiol may modulate vascular endothelial functions and angiogenic and steressor factors synthesis. E2 is synthesized by placenta in big amount during pregnancy and causes angiogenesis and vascular dilation [38]. Indeed, E2 induces NO synthesis [39–41] and angiogenic factors levels, as vascular endothelial growth factor (VEGF) and placental growth factor inhibits Tumor Necrosis Factor-α (TNF-α) synthesis by macrophages [42]. A number of recent studies with usage of up date analytical methods of investigation found low levels of estrogens in women with preeclampsia [43].

Pillar et al. conducted an investigation, aimed at detection of reliable markers of early preeclampsia and GD joining, which is based on research of micro RNA (miRNAs) in pathogenesis and their probable role as early biomarker of listed above pregnancy complications. Specific miRNAs are induced by hypoxia and in case of preeclampsia their regulation is often altered. So, probably these miRNAs mediate complications of placental hypoxia in case of preeclampsia. miRNAs, adipose tissue and insulinresistancy also play an important role in pathophysiology of GD. A number of investigations identified the highest expressed miRNAs, MiR–210, that are present in placenta and are predominantly synthetized by trophoblast cells and proved their role in control of trophoblast invasion and proliferation. The determination of placenta expressed miRNAs in maternal plasma indicates their potential role in non invasive prenatal diagnostics and indicates the type of therapeutic tactics [44].

Intravascular inflammation is observed in women with preeclampsia and small for gestational age fetuses (T helper-1 (Th-) mediated immune response). There is controversy about T-helper activity (Th-2) in women with preeclampsia and small for gestational age. CD30, one of the tumor necrosis factor receptor, is predominantly expressed in vitro and in vivo by activation of T cells, that produce cytokines of type Th2. The investigators propose to use their soluble form (sCD30) as a Th2 immune response index [45].

A MOLECULAR THEORY OF PREECLAMPSIA

Nowadays a molecular theory of preeclampsia development is widely investigated. In order to investigate the molecular interactions, the researchers used the systems of biological approach and different so called “omics”, the results of clinical, placental and functional investigations of women with adverse preeclampsia phenotype. During investigation of proteome of these pregnant in first trimester the alteration in the levels of renin-angiotensin and immune system, complement and coagulation cascade in patients with at term and early preeclampsia. Also in blood of these patients in first trimester in vitro dysregulation of trophoblast invasion was found. Due to placental transcriptomics of women with preterm preeclampsia specific genes that are associated with morbidity of mother and kids were found. “Virtual” liquid biopsy of placenta revealed that gene alterations occur in first trimester in case of these diseases. Investigations in vitro showed that hypermethylation of DNA in regulatory area ZNF554 causes suppression of gene and disturbances of trophoblast invasion, activation of BCL6 and ARNT2 sensitizes trophoblast to ischemia and pre term preeclampsia. The results of epidemiologic investigations show, that pregestational disease of mother or disturbances of immune relationships of mother-fetus-placenta play the major role in preeclampsia development. Careful study of these up to date mechanisms in «molecular phase» of preeclampsia and determination of main molecules may enable a molecular investigation.
of patients with a typical preeclampsia development phenotype [46].

CONCLUSIONS
As the incidence of Great Obstetrical Syndromes unfortunately still remains high it is crucial do find effective methods of prognostication of these states in order to influence pathophysiological mechanisms and decrease maternal and fetal morbidity and mortality. The effectiveness of combined evaluation of clinical, instrumental and serological markers in I trimester in order to prognosticate early onset preeclampsia rather high.

REFERENCES


Conflict of interest:
The Author declare no conflict of interest.

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