ABSTRACT

Introduction: Hypertension (HTN) remains the most frequent complication of pregnancy. According to WHO, it affects up to 7% of all pregnancies. Each year in Poland HTN is diagnosed in roughly 30 thousands of pregnant women; it increases the risk of complications (including risk of death) in both mother and the newborn. The maternal risks include: eclampsia, placental abruption, HELLP and DIC syndromes, acute kidney injury, congestive heart failure, pulmonary edema, liver failure. Neonatal risks include: acute and chronic hypoxia, intrauterine growth retardation, prematurity and intrauterine death.

The studies suggest that complications of HTN in pregnancy may be associated with up to 15% of all deaths of pregnant women - this is the second most frequent cause of death after thromboembolic complications.

Several classifications of HTN in pregnancy emerged over last decades. The contemporary classification of the ASC/ASH published in the year 2018 divides this disease into the following categories:

1. Chronic HTN: present before pregnancy or developing before 20th gestational week; usually lasts more than 6 weeks following delivery. Proteinuria may be present.

2. Pregnancy - associated HTN: develops after 20th gestational week and usually resolves within 6 weeks following delivery.

3. Chronic HTN with superimposed pregnancy-induced HTN proteinuria.

4. Preeclampsia: pregnancy - associated HTN with significant proteinuria, defined as > 0.3 g/24 hours or urinary albumin-to-creatinine ratio (UACR) ≥ 30 mg/mmol.

5. HTN not classified before delivery: HTN diagnosed after 20th week of pregnancy, when the HTN status before pregnancy uncertain.

Upon planning of this dissertation the ESH/ESC 2007 guidelines were effective; contemporary update of these guidelines, published in 2018 and followed by the guidelines of the Polish Society of Hypertension are largely similar and only minor changes were made concerning the diagnosis and treatment of HTN in pregnancy. According to the European guidelines HTN in pregnancy may be diagnosed if in two independent measurements at least six hours apart the blood pressure (BP) values exceed 140/90 mmHg or in any case of any value of ≥ 170/110 mmHg.

Preeclampsia is a systemic disease that affects up to 3% - 5% of all pregnancies with HTN and proteinuria as key clinical symptoms. Typically develops after the 20th gestational week, most frequently at the end of pregnancy. Preeclampsia may also be diagnosed in hypertensive women without proteinuria if one or more of the following are present: low platelet count (PLT < 100 000/μl),

impaired liver function (elevated activity of aminotransferases), acute kidney injury (with serum creatinine exceeding 1.1 mg/dl), pulmonary edema or central nervous system disorders. According to the ESC/ESH 2007 guidelines significant proteinuria was defined as > 500 mg/24 hours or > 300 mg/l. (in 2018 guidelines - as proteinuria of > 300 mg/24 hours or UACR > 30 mg/mmol).

Th pathological background of pregnancy-associated HTN and preeclampsia is multi-factorial. The risk factors for their development may be divided into non-modifiable (family history of HTN - especially during pregnancy, HTN complicating previous pregnancies, HTN in primipara, multi-fetal pregnancy, low birthweight of pregnant woman, black race) and modifiable (overweight and obesity, extremes of age at conceiving, atherogenic lipid profile, low socio-economic status, presence of anti-phospholipid antibodies, mechanical contraception, diabetes, HTN in pre-conception period, diseases of the kidney, liver and thyroid gland, SLE, hyperhomocysteinemia, trophoblastic disease, immunovasculitis, thrombophilia, cardio - vascular disease, polycystic ovary syndrome, cholestasis of pregnancy, urinary tract infection during pregnancy and assisted reproduction techniques). HTN and preeclampsia may also have genetic background: risk of both complications is higher in women born to mothers who suffered from HTN and preeclampsia, respectively. Certain nutritional deficiencies may also influence the risk of preeclampsia: for example low intake of calcium is associated with higher risk of pregnancy - induced HTN, whereas no association was demonstrated between vitamin C, E and D or polyunsaturated ω – 3 fatty acids and the risk of eclampsia.

Currently the impaired placental implantation and abnormal cytotrophoblast invasion into myometrium were identified as two key mechanisms leading to preeclampsia. This leads further to insufficient dilatation of spiral arteries, impaired placental perfusion and function early in the course of pregnancy. Described abnormalities influence on the synthesis of several vasoactive substances, crucial for normal endothelial function. During pregnancy complicated by HTN synthesis of thromboxane A2 is increases, whereas prostacyclin an nitric oxide (NO) - decreased. Expression of adhesion molecules ICAM - 1,VCAM - 1, P and E- selectins as well as synthesis and release of proinflammatory cytokines IL- 12, IL - 18, IL - 6, IL - 10, TNF α, INF - γ are markedly increased in the course of preeclampsia. Enhanced activation of the immune system is also related to the activation of endothelium by the syncytiotrophoblast cells circulating in the maternal blood. Two angiogenesis-related proteins are now considered biomarkers that reflect the activity of preeclampsia and may potentially be used as predictors of its development: sFlt - 1, s - endoglin, PIGF and VEGF. They can be assayed in urine and blood of pregnant women. Soluble tyrosin kinase Flt - 1plays important role in regulating the endothelial function and angiogenesis during pregnancy. sFlt binds circulating VEGF and PIGF, thus limiting its availability and impairing the process of angiogenesis. Nevertheless, despite of great progress in research on the pathogenesis of preeclampsia several mechanisms of its development are still not well understood.

It has been showed that women who experienced HTN or preeclampsia during pregnancy are exposed to higher risk of: long - term HTN , coronary artery disease, stroke or chronić kidney disease in the future life. Preeclamptic women have also higher risk of death due to cardio-vascular complications. The ESC/ESH guidelines also emphasize the higher CV risk in women who experienced preeclampsia. According to the ESC/ESH experts, several health challenges during pregnancy provide an insight for identifying the potential health risks, also for the future. The long - term data clearly indicate that eclampsia may be considered as risk factor of future cardio - vascular and cerebro - vascular events. Experiencing preeclampsia increases the risk of coronary artery disease by factor 2, the risk of stroke and thromboembolic events; risk of permanent HTN in future is even four times higher as compared to women with uncomplicated pregnancy. The highest risk applies to those women who experience preeclampsia early during pregnancy, i.e. before 32nd week of gestation, or pregnancy was complicated by intrauterine growth retardation or fetal death. In fact, all circumstances accompanying pregnancy - associated HTN, i.e. preeclampsia, eclampsia, HELLP syndrome, proteinuria, are considered risk factors for the future CV episodes.

The aims of the study were as follows:

1. Complex analysis of pre-pregnancy risk factors that may potentially predispose to the development of preeclampsia.

2. Assessment of the risk of development of 'permanent' HTN, chronic kidney disease (CKD) and metabolic disorders (diabetes, obesity) 5 - 10 years following the pregnancy complicated with preeclampsia as compared to healthy controls and women with HTN preexisting before pregnancy (except for HTN).

3. Analysis of the outcome of newborns delivered by preeclamptic women as compared to the healthy controls and women with HTN preexisting before pregnancy.

4. Comparison of the study group (women with preeclampsia and preexisting HTN) and control group (women with uncomplicated pregnancy) in terms of: prevalence of HTN, BP values (office and ABPM), prevalence and severity of proteinuria, renal function, glycaemia and lipid profile, and common - carotid artery intima-media thickness (CCA-IMT) 5 - 10 years after pregnancy being analyzed as a 'baseline' (starting) event.

Materials and methods: 50 patients hospitalized for the delivery (and complications of pregnancy, if applicable) in the Department of Obstetrics in the Regional Hospital in Olsztyn comprised the study group. Patients were identified in the hospital database. 200 eligible women who experienced preeclampsia 5 - 10 years earlier and were hospitalized in our hospital were identified and invited to this study, however only 50 (25%) responded to our invitation. For the diagnosis of preeclampsia the

following criteria proposed by the ESC/ESH 2007 guidelines were applied for the diagnosis of preeclampsia:

1. Systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg found in woman after 20 th week of gestation (who was normotensive before the pregnancy of interest) and one or more of the following:

2. Proteinuria > 500 mg/24 hour urine collection and/or > 300 mg/l and/or dipstick proteinuria of at least ++

3. Low platelet count (< 150 000/μl)

4. Serum creatinine > 1,1 mg/dl or doubling of baseline serum creatinine during pregnancy in women with preexisting CKD.

5. Abnormal aminotransferase activity.

6. Episode of pulmonary edema.

7. Clinical symptoms: headache, blurred vision, pain/dullness in right hypogastric region.

8. Symptoms of disturbed fetal well-being (intrauterine growth retardation, centralization of circulation, placental insufficiency).

In women with preexisting (chronic) HTN superimposed preeclampsia was diagnosed if additional proteinuria and/or organ dysfunction developed after 20th week of pregnancy.

All invited women were informed about the aim and scope of the study before any procedure was done; signed informed consent was also obtained from each study participant (both study group and control group). Women were asked to answer the questionnaire that contained questions concerning: family history, medical history, BP values before and during pregnancy, pregnancy duration, mode of delivery, anthropometric parameters of woman before pregnancy, birthweight and body length of the newborn, present age, body weight and development of a child, with possible development abnormalities). All personal data were anonymized and fully protected. If available, questionnaire data were also verified with medical documentation from hospital database and medical history files. 25 women with the history of uncomplicated pregnancy were also invited as a control group – all the procedures applied to the preeclamptic women were also applied to the control group. Full physical examination was performer on the study visit.

The following lab tests were performer in all study participants: full peripheral blood morphology, serum glucose, urea, creatinine, hsCRP, uric acid, triglycerides, total, LDL, HDL - cholesterol. eGFR was calculated based on the MDRD formula. Albumin and creatinine were also assayed in the morning urine sample and UACR was calculated. Office BP was measured on both arms, and then - three times on the arm with the higher BP values. MAP was calculated. CCA - IMT was also measured using

ultrasound and ABPM monitoring was performer. All available ABPM parameters were derived: mean 24- hour, awake (daily) and nightly BP were analyzed; MAP, heart rate (HR) and pulse pressure (PP) were obtained. Based on ABPM the BP load and BP profile (dipper-status) were also analyzed.

RESULTS: Preeclampsia significantly shortened the duration of pregnancy and influenced the APGAR score result at the delivery. Both body weight and length were lower in newborn from women with preeclampsia.

Women with HTN preexisting before pregnancy were characterized by the highest body weight and BMI before pregnancy of interest.

It has been demonstrated that the highest mean SBP and DBP values were highest among women with pre - existing HTN, as compared to those with pregnancy-induced HTN. SBP and DBP in women with chronic (pre - existing) HTN were in the 'high-normal' range on the study visit.

Mean CCA-IMT was within the normal range (< 0.9 mm) in all subjects (i.e. study and control groups), it was however higher in patients who experienced preeclampsia as compared to healthy women. BP values obtained in ABPM (including mean-24-hour, daily and nightly SBP and DBP) were significantly higher in study group vs control. The highest 24- hour, daily and nightly SBP and DBP values obtained from ABPM were found in women with preexisting HTN; the same holds true for MAP.

24-hour SBP load was higher in study patients vs control. SBP load exceeding 50,5% was highest in preexisting HTN as compared to those with pregnancy - induced HTN or control women. In turn, all subjects, i.e.study and control groups maintained dipping status on the BP profile and no difference regarding this parameter was identified between groups.

Concerning the lab test results, no patient was found to have serum creatinine exceeding 0.9 mg/dl, or eGFR below 83 ml/min./1.73 m^2. The differences in creatinine or eGFR were on - significant between groups, although the highest mean SCr was found in patients with preexisting hypertension. Similar finding applied also to uric acid.

UACR, the marker essential to identify the risk of the future CVD and/or CKD significantly differed between the groups. UACR was normal, i.e. below 30 mg/g (mean value of 25,9 mg/g) only in healthy women. In the study group (women with HTN) mean UACR equalled 169.9 mg/g and was significantly higher as compared to control group, being the highest in patients with HTN diagnosed before the pregnancy of interest (mean 568.1 mg/g) and only marginally elevated in those who experience preeclampsia (mean 30.1 mg/g).

All components of lipid profile that may adversely impact on CV prognosis were abnormal in women with HTN during pregnancy (pregnancy-induced or preexisting). This applied to total and LDL cholesterol which were higher, and HDL - cholesterol, which was lower in subects vs controls. Fasting serum glucose level was slightly (non - significantly) higher in women with preexisting HTN, but was otherwise normal in all groups.

hsCRP was higher in preeclamptic women as compared with those with preexisting HTN and controls.

CONCLUSIONS

Obtained results allowed to draw the following conslusions:

1. The high BMI, preexisting hypertension, family history of preeclampsia have been identified in this study as the main risk factors for preeclampsia.

2. Preeclampsia shortens duration of pregnancy and negatively affects the clinical condition of newborns immediately after delivery, but does not have a significant impact on their development after 5 - 10 years.

3. Preeclampsia and hypertension during pregnancy are important risk factors for subclinical kidney damage at 5 - 10 years after delivery:

a. in patients with previous preeclampsia and pregancy induced hypertension, kidney damage is manifested by hyperfiltration and microalbuminuria

b. in patients with previous preeclampsia and chronic hypertension kidney damage is manifested by macroalbuminuria, significantly lower glomerular filtration rate (remaining in the low normal range) as compared to the controls

4. Preeclampsia does not lead to the development of arterial hypertension in 5 - 10 years following delivery, but the arterial blood pressure values (remaining in the high normal range) are significantly higher than in the control group.

5. The study showed the more pronounced anthropometric and biochemical markers for metabolic syndrome in patients with preexisting hypretension and preeclmapsia than in the control group at 5 - 10 years after delivery,

6. The common carotid artery intima media complex thickness, the subclinical atherosclerosis marker, remains within the normal range, but is significantly higher in patients with pregnancy

7. There is a need to monitor the health status of women with history of hypertension during their pregnancy and to implement appropriate prophylaxis and therapy. These should be done no later than 5 years after the delivery.