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**PREGNANCY INDUCED HYPERTENSION AND NEONATAL GROWTH**

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**Abstract:** Pregnancy-induced hypertension (PIH), especially preeclampsia, is a major cause of maternal and perinatal morbidity and mortality worldwide. The impact of PIH on birth outcomes has not been extensively studied. PIH has been confirmed to increase significantly the risk of low birth weight by both increasing preterm birth as well as reducing fetal growth. Low birth weight or IUGR babies have been associated with the occurrence of several chronic diseases in later life. However, to date, there have been few studies on the effects of PIH on infant growth and neonatal wellbeing.

The **purpose** of this study was to evaluate the fetal growth and wellbeing of newborns born of mothers with confirmed pregnancy induced hypertension.

**Material and methods:** This was prospective observational study during the period of the last year, 1<sup>st</sup> of July 2018 up to the end of June 2019 conducted at the University Clinic for Gynecology and Obstetrics in Skopje. As pregnancy induced hypertension is defined the condition of blood pressure equal to or greater than 130/90 mmHg on more than two occasions greater than six hours apart without proteinuria after 21 weeks of gestation. All other more severe conditions are defined as pre-eclampsia or eclampsia. As outcome was considered the birth weight, gestational age and white blood cells count. IUGR was defined as birth weight below the tenth percentile of expected weight for gestational age. Also maternal age and BMI were considered as conjoined risk factor for the birth weight.

**Results:** In this study, 4726 newborns were born at the University Clinic for Gynecology and Obstetrics, and for analysis were considered 4273 newborns who were late preterm (35 and 36 gestational weeks) or term newborns. Two groups were evaluated: control group of 200 consecutively born newborns (late preterm and term) of healthy mothers and 100 newborns (late preterm and term) consecutively born of mothers with confirmed diagnosis of PIH, which constituted the study group. Within the control group, the proportion of Small for Gestational Age-SGA was 6,3%, and in the group of mothers with PIH was 9,5% ( $p < 0,05$ ). The maternal mean age of the hypertensive mothers was  $(32.8 \pm 5.0)$  years while that of normotensive mothers was  $(26.6 \pm 3.7)$  years, and there was not statistical significance ( $p > 0.05$ ). The Body Mass Index was higher in hypertensive mothers, compared to the healthy mothers  $(31,3 \pm 2.02$  vs.  $27.8 \pm 2.8$ ). The mean gestational age of the study group was  $(35.8 \pm 1.8)$  weeks compared to that in control group  $(37.4 \pm 1.2)$  weeks. The number of White Blood Cells (WBC) count in newborns of hypertensive mothers was  $21.4 \pm 5.3 \times 10^9/L$  compared with the control group,  $18.5 \pm 3.12 \times 10^9/L$  ( $p = 0.005$ ). Neonatal thrombocytopenia was found in 32% of neonates of preeclamptic mothers while it's found only in 9.5% of neonates in control group  $p < 0,002$ .

**Discussion:** The limitation of this study was the lack of data about maternal smoking, life style, etc. There is limited number of studies examining the correlation between fetal growth and PIH, and every information is of great value. The fact is that this condition can progress in more severe degree of hypertension and deleterious effects on the mother itself and on her child, if not treated on time.

**Conclusion:** A change in infant growth of the IUGR baby itself (e.g. catch-up growth) such as in the critical early infant period may also have long-term effects on health later in life, and this change of postpartum growth may be influenced by PIH. Therefore, it is important to study postpartum infant growth patterns of babies born to mothers with PIH, and to determine if there are differences in infant growth between babies with and those without IUGR. And, the most important action is to monitor and treat pregnancy induced hypertension and prevent more severe condition of pre-eclampsia.

**Keywords:** Small for gestational age newborn, term newborn, pregnancy induced hypertension

## 1. BACKGROUND

**Gestational Hypertension** also referred to as **Pregnancy-Induced Hypertension (PIH)** is a condition characterized by high blood pressure during pregnancy. Hypertension during pregnancy affects about **6-8% of pregnant women**. High blood pressure can present itself in a few different ways during pregnancy.

Pregnancy-induced hypertension (PIH) is defined as systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) >90 mmHg. It is classified as mild (SBP 140-149 and DBP 90-99 mmHg), moderate (SBP 150-159 and DBP 100-109 mmHg) and severe (SBP  $\geq$  160 and DBP  $\geq$  110 mmHg). The basic classification was retained, as it describes four types of hypertensive disease: 1. Gestational hypertension. 2. Preeclampsia and eclampsia syndrome. 3. Chronic hypertension of any etiology. 4. Preeclampsia superimposed on chronic hypertension. These degrees of PIH are commonly accepted.<sup>24</sup>

**The following women may have an increased risk of developing gestational hypertension:**

- First-time delivery
- Women whose sisters and mothers had PIH
- Women carrying multiples
- Women younger than age 20 or older than age 40
- Women who had high blood pressure or kidney disease prior to pregnancy

Hypertension can prevent the placenta from getting enough blood. If the placenta doesn't get enough blood, the fetus gets less oxygen and food. This can result in low birth weight. Most women still can deliver a healthy baby if hypertension is detected and treated early. In most of the Clinical Guidelines low dose Aspirin is recommended to keep the placenta vascularized, confirmed also by Bujold.<sup>25</sup> If the hypertension is severe, it can lead to Preeclampsia, which can have much more serious effects on both, mother and the baby. Very often it is necessary to deliver the baby as earlier as serious damage has not been effected, and there are some data of better prognosis in the studies from Broekhuijsen and Cluver.<sup>26,27</sup>

Women with PIH are at a greater risk of abruptio placentae, cerebrovascular events, organ failure and disseminated intravascular coagulation. Fetuses of these mothers are at greater risk of intrauterine growth retardation, prematurity and intrauterine death. Pregnancy-induced hypertension (PIH), especially preeclampsia, is a major cause of maternal and perinatal morbidity and mortality worldwide.

Preeclampsia changes the intrauterine environment of the fetus, and the fetus has to adapt to living in the unfavorable environment.<sup>28</sup> These effects include an increased neonatal mortality and morbidity; intrauterine growth restriction; premature birth; hematological abnormalities, such as thrombocytopenia, polycythemia, and neutropenia; necrotizing enterocolitis; bronchopulmonary dysplasia.

The impact of PIH on birth outcomes has not been extensively studied. PIH has been confirmed to increase significantly the risk of low birth weight by both increasing preterm birth as well as reducing fetal growth. These findings suggest that PIH, more specifically preeclampsia, is a heterogeneous syndrome and that preeclampsia may appear in two forms: restricted fetal growth preeclampsia and normal fetal growth preeclampsia. PIH may have different short term effects on infant growth between these possible two types of preeclampsia by intrauterine growth restriction (IUGR). Low birth weight or IUGR babies have been associated with the occurrence of several chronic diseases in later life. However, to date, there have been few studies on the effects of PIH on infant growth.

Several hematological abnormalities are associated with the preeclampsia syndrome. Among those commonly identified is thrombocytopenia, identified in many of the research papers, as for example by Kalagiri,<sup>29</sup> which at

<sup>24</sup> Mohammed Al-bahadily AJ, Mohammed Al-Omrani AA, Mohammed M. (2017). The Effect of Pregnancy Induced Hypertension on Complete Blood Count of Newborn. *Int J Pediatr*, 5(9): 5667-76. DOI: 10.22038/ijp.2017.24865.2101

<sup>25</sup> Bujold E, Roberge S, Nicolaides KH. (2014). Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation. *Prenatal Diagnosis*, 34(7):642-8.

<sup>26</sup> Broekhuijsen K, Van Baaren GJ, Van Pampus M, Ganzevoort W, Sikkema M, Woiski M, et al. (2015) Immediatedelivery versus expectant monitoring for hypertensivedisorders of pregnancy between 34 and 37 weeks of gestation(HYPITAT-II): an open-label, randomised controlled trial, *Lancet*;385:2492-501

<sup>27</sup> Cluver C, Novikova N, Koopmans CM, West HM. (2017) Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term. *Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No.: CD009273. DOI: 10.1002/14651858.CD009273.pub2

<sup>28</sup> Kintiraki E, Papakatsika S, Kotronis G, Goulis DG, Kotsis V. (2015) Pregnancy-Induced hypertension. *Hormones (Athens)*. Apr-Jun;14(2):211-23. doi: 10.14310/horm.2002.1582.

<sup>29</sup> Kalagiri RR, Choudhury S, Carder T, et al. Govande V, Beeram MR, Uddin MN. (2016). Neonatal Thrombocytopenia as a consequence of Maternal Preeclampsia. *AJP Rep*; 6(1):42-7. doi: 10.1055/s-0035-1565923

times may become severe enough to be life-threatening. Neonatal thrombocytopenia defined as a platelet count less than 150,000/ $\mu$ L based upon the definition used in adults. The pathogenesis of thrombocytopenia among infants born to mothers with preeclampsia is presently unknown. The principal mechanism postulated is that preeclampsia and the resultant fetal hypoxia have a direct depressant effect on fetal megakaryocytopoiesis and platelet production the combined effect of impaired megakaryocyte formation and increased platelet activation mediated through cytokines, thrombopoietin, and interleukin-6 are said to be the most likely causative mechanisms<sup>30</sup>. Low White Blood Cell Count and specifically Neutropenia is a common hematologic disorder in the newborn, particularly in preterm neonates, and SGA babies as shown in research done by Christensen.<sup>31</sup> Although its cause varies, a significant proportion of the episodes are associated with the pregnancy complicated by preeclampsia. Neonates delivered to women with preeclampsia have a 50% incidence of neutropenia (defined as absolute neutrophil count less than 500  $\mu$ L). Neutropenia has a variable course, typically lasting days to weeks in affected infants. The biological mechanism for preeclampsia resulting in neonatal neutropenia has not been fully elucidated.<sup>32</sup> Intrauterine Growth Restriction (IUGR) is defined as birth weight less than 10th centile for gestational age. Infants with IUGR or Small for Gestational Age (SGA) are at increased risk of perinatal morbidity and mortality. They also have higher rates of physical, neurological and mental impairment than babies with appropriate intrauterine growth. Fetal growth is a useful marker for fetal well-being. Pregnancies complicated by IUGR, defined as a pathological process of reduced fetal growth, have been associated with an increase in perinatal mortality. Preeclampsia is a significant risk factor in the development of IUGR and represents the most common cause of IUGR in the non-anomalous infant. Therefore, the **purpose** of this study was to evaluate the fetal growth of newborns born of mothers with confirmed pregnancy induced hypertension.

## 2. MATERIAL AND METHODS

This was prospective observational study during the period of the last year, 1<sup>st</sup> of July 2018 up to the end of June 2019 conducted at the University Clinic for Gynecology and Obstetrics in Skopje. As pregnancy induced hypertension is defined the condition of blood pressure equal to or greater than 140/90 mmHg on more than two occasions greater than six hours apart without proteinuria after 21 weeks of gestation. All other more severe conditions are defined as pre-eclampsia or eclampsia. As outcome was considered the birth weight and gestational age. IUGR was defined as birth weight below the tenth percentile of expected weight for gestational age. Also maternal age and BMI were considered as conjoined risk factor for the birth weight.

Any babies with anemia at birth, ABO and Rh incompatibility, twins, severe birth asphyxia or congenital malformation were excluded from this study. Also babies born to mothers who have an acute illness like antepartum hemorrhage and chronic illness likely to cause changes in hematological profile like severe anemia, connective tissue disorders, diabetes mellitus and chronic hypertension were also excluded from the study. Clinical Parameters Maternal details including age, parity, time of delivery, and mode of delivery or any complications during labor were also recorded. Details of the baby including sex need for resuscitation; Apgar score, birth weight and gestational age (by modified Dubowitz scoring) were recorded. According to normal hematological values in infancy and childhood hematological parameters (white blood cells count and thrombocytes) have been studied. The statistical analysis was performed using Chi-square test. The lower level of accepted statistical significant difference is equal or below 0.05.

## 3. RESULTS

In this study, 4726 newborns were born at the University Clinic for Gynecology and Obstetrics, and for analysis were considered 4273 newborns who were late preterm (35 and 36 gestational weeks) or term newborns. Two groups were evaluated: control group of 200 consecutively born newborns (late preterm and term) of healthy mothers (without any known risk factor bad neonatal outcome) and 100 newborns (late preterm and term) consecutively born of mothers with confirmed diagnosis of Pregnancy Induced Hypertension (PIH) which

<sup>30</sup> Hoffbrand AV, Higgs DR, Keeling DM, Mehta AB. (2015). Postgraduate Haematology. Wiley 2015, Chapter 50, pp. 870-84. ISBN: 978-1- 118-85432-7

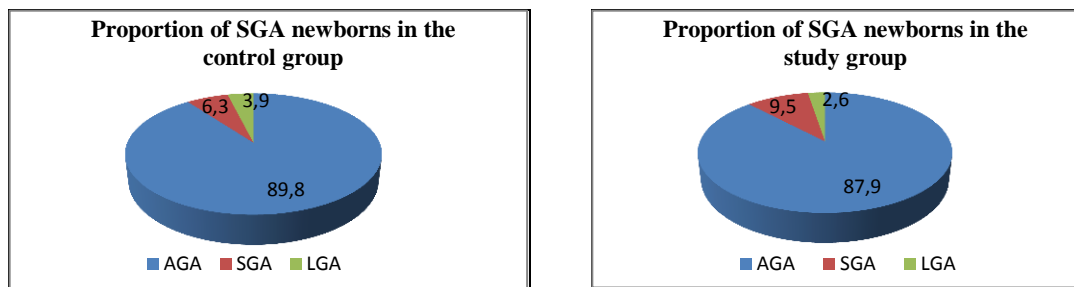
<sup>31</sup> [Christensen RD, Yoder BA, Baer VL, Snow GL, Butler A. \(2015\) Early-Onset Neutropenia in Small-for-Gestational-Age Infants. \*Pediatrics\*, 136\(5\):e1259-67. doi: 10.1542/peds.2015-1638. Epub 2015 Oct 12.](#)

<sup>32</sup> Prekshya L Prakash, P Sunil Kumar, M Venkata Murthy, KR Haricharan. (2015). Assessment of hematological profile of newborn at birth, born to mothers with gestational hypertension, preeclampsia and eclampsia syndrome. *Journal of Evolution of Medical and Dental Sciences*, Vol2, Issue 34, August 26; Page: 6360-6369.

constituted the study group. Detailed patients' histories were evaluated, and maternal interviews conducted, to get better insight in their condition.

Within the control group of newborns, the proportion of Small for Gestational Age-SGA (those who had Intrauterine Growth Restriction) was 6,3%, and in the group of mothers with PIH was 9,5% (Figure 1). The difference has statistical significance ( $p<0,05$ ).

**Figure 1. Proportion of the Small for Gestational Age newborns in both groups**



\*AGA= Appropriate for gestational age      SGA= Small for gestational age      LGA=Large for gestational age

The maternal mean age of the hypertensive mothers was (32.8±5.0) years while that of normotensive mothers was (26.6±3.7) years. The majority of the mothers were between (20 – 30) years old (54% of hypertensive mothers and 84% of normotensive mothers) but due to the small number of participants, there was not statistical significance ( $p>0.05$ ). The Body Mass Index was higher in hypertensive mothers, compared to the healthy mothers (31,3±2.02 vs. 27.8±2.8)

The mean gestational age of the study group was (35.8±1.8) weeks which is lower than the gestational age of the control group (37.4±1.2) weeks. It is well known that the number of White Blood Cells (WBC) count is usually higher in newborns of hypertensive mothers, and in our study the difference was statistically significant (in the study group the WBC count was 21.4±5.3x10<sup>9</sup>/L compared with the control group, 18.5±3.12x10<sup>9</sup>/L ( $p=0.005$ )). Neonatal thrombocytopenia was found in 32% of neonates of preeclamptic mothers (who had more severe degree of PIH) while it's found only in 9.5% of neonates of healthy mothers, and  $p<0,002$ .(Table 1)

**Table-1: Comparison between the mean neonatal profile of the study and control groups**

	Newborns of healthy mothers	Newborns of mothers with PIH	p value
Maternal age (mean±SD)	26.6±3.7	32.8±5.0	N.S.
Maternal Body Mass Index	27.8±2.8	31,3±2.02	$p<0,05$
Mean gestational age	37.4±1.2	35.8±1.8	$p<0,05$
Sex male/female			
WBC count	18.5±3.12x10 <sup>9</sup> /L	21.4±5.3x countx10 <sup>9</sup> /L	$p<0,005$
Neonatal thrombocitopenia	9,5% in the group	32% in the group	$p<0,002$
5-minute Apgar score	9.44±0.7	8.62±1.7	N.S.

#### 4. DISCUSSION AND CONCLUSION

Pregnancy induced hypertension is one of the most common causes of both maternal and neonatal morbidity. A newborn delivered to mothers with hypertension are more liable for intrauterine growth restriction and may be delivered prematurely, confirmed in a Cochrane systematic review.<sup>33</sup> The limitation of this study was the insufficient data about maternal smoking, life style, etc. There is limited number of studies examining the correlation

<sup>33</sup> Razak A, Florendo-Chin A, Banfield L, Abdul Wahab MG, McDonald S, Shah PS, Mukerji A. (2018). Pregnancy-induced hypertension and neonatal outcomes: a systematic review and meta-analysis. *J Perinatol*.38(1):46-53. doi: 10.1038/jp.2017.162. Epub 2017 Nov 2.

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between fetal growth and PIH, and every information is of great value. The fact is that this condition can cause more severe hypertension and deleterious effects if not treated on time.

### CONCLUSION

A change in infant growth of the IUGR baby itself (e.g. catch-up growth) such as in the critical early infant period may also have long-term effects on health later in life, and this change of postpartum growth may be influenced by PIH. Therefore, it is important to study postpartum infant growth patterns of babies born to mothers with PIH, and to determine if there are differences in infant growth between babies with and those without IUGR. And, the most important action is to monitor and treat pregnancy induced hypertension and prevent more severe condition of pre-eclampsia. It is concluded that babies of the mothers with pregnancy induced hypertension are more more liable to be premature and to have lower body weight for gestational age, low Apgar score. Neonates of hypertensive mothers are more liable to have lower WBC and thrombocytopenia and this risk increase when the mothers develop preeclampsia. It could be recommended encouraging regular antenatal care for more effective preventive and therapeutic measures of pregnancy induced hypertension. And for further research, large population based studies are recommended in order to determine the scope of this problem nationwide and include more associated factors.

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