ICASH-A060

SYSTEMATIC REVIEW METABOLIC DISRUPTION IN GESTATIONAL HYPERTENSION DISORDER

Diyas Windarena*, Siti Nurharisah, Benigna Maharani, Mardiyono Mardiyono

Master of Applied Science in Midwifery, Poltekkes Kemenkes Semarang, Indonesia

*Corresponding authors' e-mail: diyaswinda@gmail.com

ABSTRACT

Background: *Gestational hypertension is one of the diseases responsible for increased morbidity and 18% of maternal deaths in the world. Gestational hypertension has complex causes and symptoms, so pathogenesis is difficult to determine. Complications of gestational hypertension will cause Preeclampsia. This study aims to explain the metabolic disorders experimented by women with gestational hypertension. This description can be used as an early detection tool for hypertension so that complications can be prevented.*
Methodology: *Searching articles for this research is done by searching in the google scholar, science direct and PubMed databases. Only full text and written by english will be included in this study. The keyword that is used "Risk Factor" or "Metabolic" and "Gestational Hypertension" or "Blood Pressure" or "Pregnancy Hypertension" with the year limit between 2009 – 2019. A systematic review of PRISMA was used in this study. The study focused on the discussion about gestational hypertension in pregnant women.*
Results: *12 research articles were foundit is known that pregnant women with gestational hypertension have serum calcium, magnesium, nitric oxide, vitamin D, cobalt and iodine which tend to be lower than normal pregnant women. Whereas cadmium levels tend to be high can stimulate oxidative stress which is able to worsen the condition leading to preeclampsia.*
Conclusion: *Health checks on pregnant women can be used as a basis for screening and treatment. Methods of checking calcium levels that allow as medium for screening in detecting the severity of hypertension and predicting disease risk.*

Keywords: *Hypertension, Pressure, pregnant women*

INTRODUCTION

Hypertension during pregnancy is one of the causes of maternal death worldwide especially indeveloping country. Hypertension in pregnancy disorders causes almost 18% of maternal deaths worldwide. An estimated 62,000 – 77,000 deaths per year. [1] In a survey conducted in 29 countries in Africa, Asia, Latin America, and the Middle East, 25 – 9% of women with severe circumstances caused effect of the complications of hypertension gestational. This complication as the direct cause of 20% of maternal deaths is reported. Hypertension gestational will threaten the well-being of the mother and fetus that underlie the occurrence of preterm birth and asphyxia in the newborn. [2] Various Sciences studied the early detection of hypertension and its treatment, but the number of occurrences is still high. This happens because hypertension gestational occur due to multi-factors that require handling in its entirety. [18]

Hypertension in pregnancy is defined as systolic blood pressure 140 mmHg or diastolic blood pressure, and more ranging from 90 mmHg or more with a measurement separate measurements at least twice with an interval of 4 to 6 hours. To diagnose hypertension can be done by measuring the blood pressure.. [13] The blood pressure is measured using a sphygmomanometer. [14] Risk factors for hypertension in pregnancy, one of which excessive weight before and during pregnancy have a very big contribution. The combined effect of large risk factors suggests that interventions that focus on these risk factors should be part of pre-treatment conceptual and pranatal. [3] Heavy forms of hypertension gestational are preeclampsia, eclampsia, HELLP syndrome we need to know country of the body of pregnant women that can aggravate the complications. [13]

By knowing the state of the abnormal metabolism in hypertensive women system gestasional complex then it would be helpful in further research. Such research can be a method to detect in order to minimize complications. Other research is determining the treatment to cope with abnormal circumstances on the metabolism of women with hypertension gestasional. On the State of the already severe, health workers can plan a comprehensive care through prenatal counseling, monitoring visits, pregnancy monitoring and timely reference intrapartum and post!, appropriately. This is the underlying need for studies regarding the mother's metabolism disorders with hypertension gestasional.

METHODS

Review on metabolic disorders in mothers with hypertension gestational systematic review uses a PRISMA. The conduct of search and selection the study was collected by using the database search google scholar, PubMed and ScienceDirect with the vulnerable publication year 2009 – 2019. The keyword that is used is the "Risk Factor" or "Metabolic" and "Gestational Hypertension" or "Blood Pressure" or "Pregnancy Hypertension". Inclusion criteria that we want to be examined are: (1) respondent is the pregnant women with hypertension or hypertension risk gestational (2) respondents who got the treatment not being having a problem other than the disease gestational (3) hypertension studies written in English and full text.

Criteria exclusion are: (1) literature that is not full (2) literature does not explain about the population or populations using animal try (3) literature that does not discuss hypertension in pregnant women (4) limitation on year also set research on publishing in the year 2009 – 2019 and each of the documents found are excluded. Database searching is done for 14 days, 1 April – 14 April 2019. Screening is done based on the appropriate titles and journals in full. The selection process documents are presented in Figure 1 from 8951 study found only 12 studies that we enter in this systematic review. The study focused on the discussion about gestational hypertension in pregnant women.

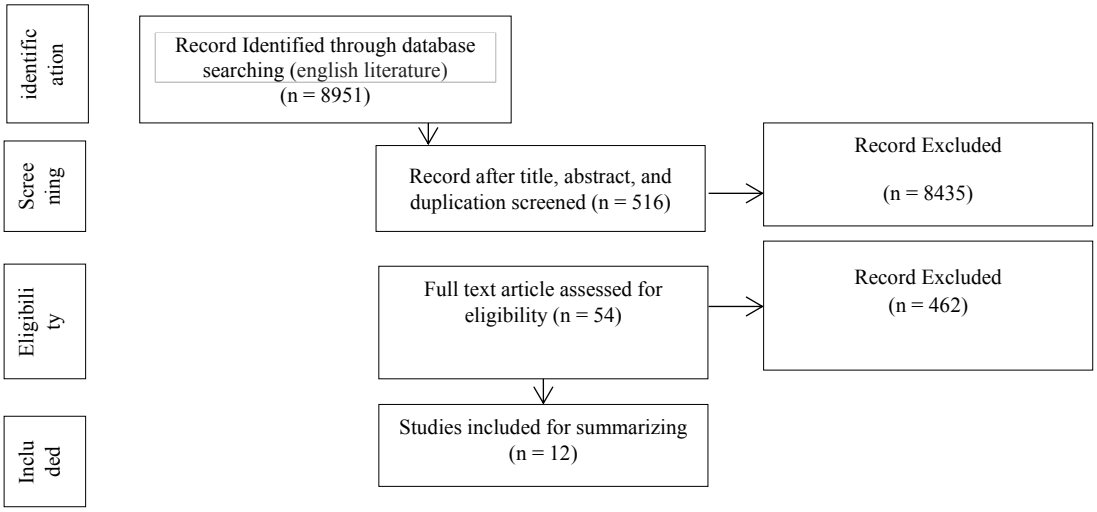

Figure 1. PRISMA flow diagram

RESULTS

Tabel 1 present the characteristics of 12 study involved in this systematic review. Study focused on the discussion about gestational hypertension in pregnant women.

Table 1. Metabolic Disordes in women with Gestational Hypertension

	Title	Author	year of publication	Methods	Results
1.	Hypocalciuria in pre-eclampsia and gestational hypertension due to decreased fractional excretion of calcium	McGrowder, D. et al.	2009	The study population is a prospective study The study was conducted in west indies between April and December 2006 Total of the sample were 83 pregnant women in the third trimester (32 weeks to term) they are is 29 with preeclampsia, 27 with hypertension and 27 normotensives.	The mean ± SD values Preeclampsia Calcium excretion rate : 1.70 ± 0.26 mmol/day Hypertensive women Calcium excretion rate : 4.23 ± 0.59 mmol/day Normotensive women Calcium excretion rate : 4.43 ±0.60 mmol/day
2.	Calcium to creatinine ratio in pregnancy-induced hypertension	Gasnier, R. et al	2012	The study population is a case-control study The study was conducted in Hospital de Clinical de Porto Alegre between March 2008 and November 2009 The sample is women between 20 and 37 weeks of gestation	Median, minimum – maximum and 25 – 75 percentile Severe PE 24 h calciuria: 81.5 mg (3 – 164) Calcium to creatinine ratio : 0.0108 mg/mg (0-0.14) Mild PE 24 h calciuria: 118 mg (8-564) Calcium to creatinine ratio : 0.05 mg/mg (0.01 – 0.36) CH 24 h calciuria: 226 mg (101 – 612) Calcium to creatinine ratio : 0.14 mg/mg (0.02-0.38)

	Title	Author	year of publication	Methods	Results
					NP 24 h calciuria: 272 mg (60-489) Calcium to creatinine ratio : 0.0995 mg/mg (0.04-0.23)
3.	Serum calcium and magnesium levels in women presenting with pre-eclampsia and pregnancy-induced hypertension: a case-control study in the Cape Coast Metropolis, Ghana	Ephraim, R.K.D., et al.	2014	The study population is Case-control study The study was conducted in three hospitals in the Cape Coast Metropolis, Ghana December 2013 – Mei 2014 Total of the sample were 380 pregnant women (≥20 weeks gestation) composed of 120 women with PIH, 100 women with PE and 160 healthy.	The mean Controls : Ca^{2+} serum were 2.385 mmol/l Mg^{2+} level was 1.643 mmol/l Hypertension : Ca^{2+} serum were 1.248 mmol/l Mg^{2+} level were 0.837 mmol/l Preeclampsia : Ca^{2+} serum were 1.168 mmol/l Mg^{2+} level were 0.688 mmol/l
4.	Maternal serum uric acid and calcium as predictors of hypertensive disorder of pregnancy: A case-control study	Kumar, N., Singh, A. K.	2019	The study population is Prospective case-control study The study was conducted in Northern India from October 2016 to May 2017 Total of the sample were 220 antenatal women ≥ 34 weeks of gestation with 110 cases having hypertensive and 110 controls with normal blood pressure.	The mean ± SD values Controls : serum uric acid was 4.42 ± 1.42 mg/dl Calcium were 8.94 ± 0.6 mg/dl Hypertension : Serum uric acid was 6.8 ± 2.72 mg/dl Calcium were 8.61 ± 0.78 mg/dl
5.	Oxidative stress increased in pregnant women with Iodine Deficiency	Vidal, Z.E.O. et al.	2014	The study population is Studi case cross-sectional The study was conducted in Mexico between April 2011 to November 2012 Total of the sample were 212 pregnant women with 15 to 48 years old	Median ± SD TM 1 : 86,9 -215,7 dan 155,7 µg/L TM 2 :104.5 – 216.5 dan 154,5 µg/L TM 3 : 111.4 – 193.7 dan 144,5 µg/L

	Title	Author	year of publication	Methods	Results
6.	Maternal early-Pregnancy thyroid function is associated with subsequent hypertensive disorders of pregnancy: the generation R study,	Medici, M. et al	2014	The study population is generation R Study population base noninterventional cohort study. The study was conducted in The Netherlands between April 2002 and January 2006 Total of the sample were 5153 women in pregnancy. (345 leads to hypertensive disorders consisting of 209 preeclampsia is136.	Mothers with hyperthyroid are at high risk of hypertension OR 3.40 (95% CI 1.46 – 7.91) P = 0.005
7.	Iodine levels are associated with oxidative stress and antioxidant status in pregnant women with hypertensive disease	Rufino, S.C. et. al	2017	The study population is a case-control study Kasus took di Mexico from January 2015 to April 2015 Total of the sample were 57 pregnant women in the last trimester of pregnancy, 20 were diagnosed with hypertensive and 37 were normotensive pregnant	Median Controls : Urinary iodine concentration (UIC) : 150 – 249 µg/l Hypertension : Urinary iodine concentration (UIC) : 50 – 149 µg/l
8.	Serum cobalt status during pregnancy and the risks of pregnancy-induced hypertension syndrome: A prospective birth cohort study	Liang, C. et al	2018	The study population is a prospective cohort study The study was conducted in China between May 2013 until September 2014 Total of the sample was 3260 pregnant women (≥ 18 years old and pregnant ≤ 14 week	The mean ± SD values Controls : Cobalt trimester 1 : 5.21 ± 0.51 Cobalt trimester 2 : 19.67 ± 0.51 Hypertension : Cobalt trimester 1: 5.95± 0.51 Cobalt trimester 2 : 5.79 ± 0.54
9.	Homocysteine, endothelin – 1 and nitric oxide in patient s with hypertensive disorders complicating pregnancy	Zeng et al	2015	The study was conducted in China between June 2012 to June 2015 Total of the sample were 239 pregnant women	Serum homocysteine and endothelin - 1 in the hypertension group tended to be significantly higher than the control group ($p < 0.05$) and would be even higher in patients who were heavier while the Nitric Oxide level in

	Title	Author	year of publication	Methods	Results
					hypertensive patients was lower than the control group (P <0 , 05) and tend to be lower in patients who are more severe.
10.	Is the first-trimester vitamin D status in nulliparous women associated with pregnancy-related hypertensive disorders?	Weert et al	2016	The study population is a prospective community-based cohort study The study was conducted in Amsterdam, the Netherlands between January 2003 to Maret 2004 Total of the sample was 2074 nullipara women without a prior history of hypertension (17 weeks)	When compared to women with normal vitamin D status, women who were deficient had an increased risk for hypertension to preeclampsia (OR 2.08; 95% Cl 1.05 - 4.13) but the association was not significant (OR 1.88; 95% Cl 0.79 - 4.48) There was no significant difference in the number of immature platelet fraction between groups with preeclampsia and hypertension in pregnancy. Different profiles in the platelet index in pregnancies with hypertension.
11.	Immature Platelet fraction in Hypertensive pregnancy	Moraes et al	2015	The study population is a cross-sectional study The study was conducted in Brazil Total of the sample was 99 pregnancy women with there are normotensive pregnancy 33, preeclampsia syndrome 34 dan hypertension pregnancy 32	When compared to women with normal vitamin D status, women who were deficient had an increased risk for hypertension to preeclampsia (OR 2.08; 95% Cl 1.05 - 4.13) but the association was not significant (OR 1.88; 95% Cl 0.79 - 4.48) There was no significant difference in the number of immature platelet fraction between groups with preeclampsia and hypertension in pregnancy. Different profiles in the platelet index in pregnancies with hypertension.

12. Cadmium body burden and pregnancy-induced hypertension	Liu, H. Et al	2018	The study population is a cross-sectional study The study was conducted in Wuhan, China between September 2012 and October 2014 Total of the sample were 5429 pregnant women 199 with hypertension	The mean ± SD values Control : Cd : 0.40 ± 1.99 µg/L Hypertension : Cd : 0.56 ± 2.71 µg/L

Of research results that calcium levels in the mother's body with preeclampsia significantly lower when compared with pregnant women who are experiencing hypertension and calcium levels averaged the highest is on the mom with normal pregnancy. [4,15] Different Things indicates that pregnant women with hypertension and lower levels of preeclampsia calcium but it was not significant. In this study described because respondents are diverse and not controlled his diet so it is estimated it's what makes the result not significant. [5]

This is in line with the results of Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) that significantly increased in women with hypertension ($p < 0.0001$) and preeclampsia ($p < 0.0001$).

Women with hypertensive disorders have a lower level of magnesium compared to the control group but not a significant result.[4]

Different results obtained result turns out the levels of uric acid and serum calcium significantly lower in mothers with hypertension in pregnancy when compared with normal pregnant women. But unfortunately, this is not the latest research examined regarding the levels of uric acid and serum calcium in the mother with preeclampsia or eclampsia. [14]

Research already try giving calcium supplements in pregnant women who are at risk of experiencing hypertension which is done in South Africa, Zimbabwe, and Argentina in July 2011 to September 2016 but the result turned out to be supplement of calcium has not significantly reduced the incidence of preeclampsia due to problems of compliance that is still lacking. [6]

Metabolic disorders that are associated with the body's calcium levels which need thyroid iodine is in process. The results obtained in the research that low iodine levels will stimulate the onset of oxidative stress on pregnant women [11] This is in line with the research that mother with hyperthyroid at high risk of experiencing hypertension in pregnancy. [17]It also on the research group on hypertension that produces urinary iodine concentration tends to be lower than normal with the pregnancy on the mother but not yet significant. [16]

However, in this report not obtained as a result of iodine levels in pregnant women with preeclampsia or eclampsia.In addition to calcium, magnesium, uric acid and iodine in a study conducted in China in May 2013 – September 2014 is obtained that the concentration of Co varies from first trimester second trimester and into the. The maternal serum concentration of Co during pregnancy negative associated with the occurrence of hypertension linearly. The concentration of Co in the second trimester also inversely proportional is associated with levels of inflammatory factors and stress factors on the placenta. So a low concentration of serum Coserum in trimester both can be meaning with the genesis of hypertension. [7]

Furthermore, in a study intake in China in June 2012 to June 2015 with respondents expecting mothers with hypertension in pregnancy serum Homocysteine results obtained and endothelin-1 in hypertensive groups tend to be significantly higher compared with the control group ($p < 0.05$) and will be higher in people with more severe while the level of nitric oxide in people with hypertension were lower than the control group ($P < 0.05$) and tend to be lower in people with the more severe. [9]

It also examined which was done in China from September 2012 to October 2014 in normal pregnant women and women with acquired hypertension results in high-risk Cd 2.2 times more likely affected by hypertension in pregnancy. In addition, it found an interaction between Cd exposure and socio-economic status of mothers with hypertension ($P = 0.04$ interaction) [8]

DISCUSSION

Lowering the death rate due to hypertension in pregnancy is a global priority. The previous report explained that pregnant women with hypertension have low serum calcium levels. [15] The latest report obtained that in addition to a decrease in the levels of calcium, there was also a decrease in levels of

nitric oxide, magnesium, vitamin D, cobalt and iodine. [4,7,9,10,11,12] To Vascular Endothelial dysfunction is currently still be key against the onset of hypertension in pregnancy and the circumstances that may aggravate such preeclampsia and eclampsia. So preventing endothelial cells from an injury effectively to prevent or cope with hypertension in pregnancy. [9]

Hcy is a sulfur amino acid metabolism results from the result of the oxidase compound tomosynthesis acid and free radicals that can cause injury to endothelial cells. Hcy increased due to the needs of the Group of vitamin B and folate intake increased but that is not enough. ET-1 is vasoconstrictor powerful peptides produced by the endothelial cells which can affect the proliferation of contractions of the blood vessels so that blood pressure increases. While NO has relaxing blood vessels and smooth muscle so when NO increases can maintain the status of the flow of blood. But the circumstances that occurred in pregnant women with hypertension is the levels of Hcy and ET-1 and NO declining following the severity. [9]

Another factor is the low amount of calcium may explain the high prevalence of hypertension in pregnancy and continues to decline while already preeclampsia. [4,6] It can interfere with the growth of the fetus because the fetus very needs calcium for bone growth. [6] A study explains when the level of serum calcium intracellular calcium levels decreased, increased, causing smooth muscle constriction of the blood vessels and can increase the resistance of the blood vessels so that blood pressure systolic and diastolic increases. [4]

Pregnant women with hypertension or preeclampsia also have significantly lower levels of magnesium compared with normal pregnant women. [4]In addition to theserum calcium levels, it turns out that the serum Co concentration of women with gestational hypertension is lower in the second trimester can be related to the incidence of hypertension in pregnancy. Low Co levels affect inflammatory and oxidative stress on the placenta because it related to antioxidants. Cobalt (Co) as an important component of vitamin B12 which is important in the regulation of blood pressure and lowers blood pressure in the heart. [7]

This is very different from the content of cadmium in the body because of the higher content of cadmium in the body of a pregnant woman, it will lead to increased risk factors 2.2 to occur in pregnancy hypertension. Cadmium (Cd) and toxic heavy metals can be released into the environment through industrial and household waste. The Cd will be absorbed in the body through food, smoking, drinking water and air. The Cd will be stored in the liver, kidney, and bone over many years. Absorption of Cd will increase if there is a deficiency of iron tends to expect on pregnant women because of its high iron needs. High Cd rate will increase the risk of hypertension due to renal dysfunction such as mechanisms, abnormalities of the immune system and oxidative stress placenta. People of low socioeconomic status generally vulnerable to the risk of exposure to due to environmental pollution such as industrial area and near the condition of life is bad. [8]

Other studies tried researching vitamin D deficiency against the incidence of hypertension in pregnant women. The active form of vitamin D (1.25 dihydroxy vitamin D –) appears to inhibit renin from renal. This suppresses Renin-Angiotensin Aldosterone System (RAAS) for maintaining blood normotensive. However, after research, it turns out that the relationship between vitamin D levels and the incidence of hypertension may exist but are not significant. [10]

In another study also obtained as a result of iodine is an important element for the synthesis of thyroid hormones and as an antioxidant enzyme induces antioxidants directly or indirectly. Iodine can be added to the double bond of some unsaturated fatty membranes of cells that make cell membranes less reactive toward free radicals and also compete with iodine radicals lipid membranes, proteins and DNA to stabilize so that the level of the cell. optimal iodine is correlated with an increased amount of antioxidants and oxidative stress. [11] Immature Platelet Fraction (IPF) in accordance with the level of production of platelets in the bone marrow. This reflects the stage of thrombosis and poiesis can be used to distinguish the cause of thrombosis cytopenia [11]. With it being more stable parameters of Mean

Platelet Volume (MPV). [12]Another factor to consider is a female with age ≥ 40th higher risk of hypertension. [4] In addition, lifestyle factors related to hypertension disorders. Women who are overweight and obese have an increased risk of hypertension disorder during pregnancy, including preeclampsia and hypertension gestational. The increased risk is reinforced in women who smoke. An increased risk of hypertension during pregnancy almost doubled in women who are overweight and 3 times larger in females of obesity when compared with women of normal weight. [19]

The thing that's been done by taking calcium supplements to increase the levels of calcium and lower blood pressure in the women with gestational preeclampsia and prevent preeclampsia.[6] If you know the description of the metabolic state of the mother with gestational hypertension, it can be used as a basis for screening and treatment. The method of checking calcium levels allows as a medium for additional screening in detecting the severity of hypertension and predicting possible diseases.[5]

The description of metabolic disorders in women with gestational hypertension is very complex. It is known that mothers with hypertension during pregnancy have decreased levels of serum calcium, magnesium, nitric oxide, vitamin D, Cobalt, Iodine and increased Cadmium. While the research that has been carried out is still focused on giving calcium supplements to pregnant women. Future studies are expected to pay attention to the situation of nitric oxide deficiency, vitamin D, cobalt, iodine and increase cadmium in the development of treatment and screening.

CONCLUSIONS

Gestational hypertension is a complication of pregnancy caused by multiple factors, one of which is metabolic disorders. It is known that pregnant women with hypertension have low levels of serum calcium, magnesium, nitric oxide, vitamin D, cobalt and iodine. Whereas cadmium is high which can stimulate oxidative stress and increase the incidence of complications in women with gestational hypertension. Future studies are expected to pay attention to other metabolic disorders such as nitric oxide deficiency, vitamin D, cobalt, Iodine and increased cadmium in the development of treatment and screening.

REFERENCES

1. Lalenoh, C.D. Preeklampsia Berat dan Eklampsia : Tatalaksana Anestesia Perioperatif. Severe (Preeclampsia and Eclampsia : Management of Perioperative Anesthesia). Yogyakarta: depublish; 2018. (Indonesian)
2. Souza, J. P., Gülmezoglu, A. M., Vogel, J., Carroli, G., Lumbiganon, P., Qureshi, Z., et.al. Moving beyond essential interventions for reduction of maternal mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study. The Lancet. (2013) 381(9879), 1747–1755.
3. Alves, E., Azevedo, A., Rodrigues, T., Santos, A. C., & Barros, H. Impact of risk factors on hypertensive disorders in pregnancy, in primiparae and multiparae. Annals of Human Biology, 40(5). (2013);377–384.
4. Ephraim, R. K. D., Osakunor, D. N. M., Denkyira, S. W., Eshun, H., Amoah, S., & Anto, E. O. Serum calcium and magnesium levels in women presenting with pre-eclampsia and pregnancy-induced hypertension: a case-control study in the Cape Coast metropolis, Ghana. BMC Pregnancy and Childbirth. (2014); 14(1).
5. Gasnier, R., Valério, E. G., Vettorazzi, J., Martins-Costa, S. H., Barros, E. G., & Ramos, J. G. L. Calcium-to-creatinine ratio in pregnancy-induced hypertension. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. (2012); 2(1), 59–64.
6. Hofmeyr, G. J. Betran, A. P. Madliki, M. S. Cormick G, Munjanja, S. P, Fawcus, S. Mose, S. Hall, D. Ciganda, A. Seuc, A. H. Et al. Prepregnancy and early pregnancy calcium supplementation among women at high risk of pre-eclampsia: a multicentre, double-blind, randomized, placebo-controlled trial. Lancet. (2019); 393: 330–39
7. Liang, C., Wang, J., Xia, X., Wang, Q., Li, Z., Tao, R., et. al. Serum cobalt status during pregnancy and the risks of pregnancy-induced hypertension syndrome: A prospective birth cohort study. Journal of Trace Elements in Medicine and Biology;(2018). *46, 39–45.*
8. Liu, H., Xia, W., Xu, S., Zhang, B., Lu, B., Huang, Z., et. al. Cadmium body burden and pregnancy-induced hypertension. International Journal of Hygiene and Environmental Health. (2018).; 221(2), 246–251.
9. Zeng Y, Li M, Chen Y, Wang S. Homocysteine, endothelin-1 and nitric oxide in patients with hypertensive disorders complicating pregnancy. International Journal of Clinical Experimental Pathology. (2015);8(11): 15275–15279.
10. Van Weert, B., van den Berg, D., Hrudey, E. J., Oostvogels, A. J. J. M., de Miranda, E., & Vrijkotte, T. G. M. Is first-trimester vitamin D status in nulliparous women associated with pregnancy-related hypertensive disorders? Midwifery.; (2016). *34, 117–122.*
11. Vidal, Z. E. O., Rufino, S. C., Tlaxcalteco, E. H., Trejo, C. H., Campos, R. M., Meza, M. N., et. al. Oxidative Stress Increased in Pregnant Women with Iodine Deficiency. Biological Trace Element Research (2014). ; *157(3), 211–217.*

12. Moraes, D., Munhoz, T. P., Pinheiro da Costa, B. E., Hentschke, M. R., Sontag, F., Silveira Lucas, L., et. al. Immature platelet fraction in hypertensive pregnancy. Platelets. (2015). ;*27(4), 333–337.*
13. Kattah, A. G., & Garovic, V. D. The Management of Hypertension in Pregnancy. Advances in Chronic Kidney Disease. (2013). ; *20(3), 229–239.*
14. Kumar, N., & Singh, A. K. Maternal serum uric acid and calcium as predictors of hypertensive disorder of pregnancy: A case-control study. Taiwanese Journal of Obstetrics and Gynecology. (2019). ; *58(2), 244–250.*
15. McGrowder, D., Williams, A., Gordon, L., Crawford, T., Lindo, R. A., Irving, R., Hamilton, M., Fraser, Y. T.P., Hypocalciuria in pre-eclampsia and gestational hypertension due to decreased fractional excretion of calcium. Archives of medical science. (2009); vol.5 Iss. 1. 80
16. Rufino, S.C., Meza, M.N., Solís, P.G., Rosas, I.X., Helguera, O.A., Iodine levels are associated with oxidative stress and antioxidant status in pregnant women with hypertensive disease. Nutrition Hospitalaria. (2017); 34(3):661-666.
17. Medici, M., Korevaar, T. I. M., Schalekamp-Timmermans, S., Gaillard, R., de Rijke, Y. B., Visser, W. E., et. al. Maternal Early-Pregnancy Thyroid Function Is Associated With Subsequent Hypertensive Disorders of Pregnancy: The Generation R Study. The Journal of Clinical Endocrinology & Metabolism. (2014). *99(12), E2591–E2598.*
18. Roberts, J. M., & Bell, M. J. If we know so much about preeclampsia, why haven't we cured the disease? Journal of Reproductive Immunology. (2013). ; 99(1-2)
19. Gudnadóttir, T. A., Bateman, B. T., Hernádez-Díaz, S., Luque-Fernandez, M. A., Valdimarsdottir, U., & Zoega, H. Body Mass Index, Smoking and Hypertensive Disorders during Pregnancy: A Population Based Case-Control Study. PLOS ONE,. (2016);11(3), e0152187.