Review Article

iMedPub Journals
www.imedpub.com

Womens Health and Reproductive Medicine

2017
Vol.1 No.1:5

Dangers to Mothers and Babies in Early Onset Hypertensive Disorders

Shakuntala Chhabra[1]* and A Singh[2]

Department of Obstetrics and Gynecology, Mahatma Gandhi Institute of Medical Sciences, Wardha, Maharashtra, India

***Corresponding author:**
Shakuntala Chhabra

chhabra_s@rediffmail.com

Department of Obstetrics and Gynaecology, Mahatma Gandhi Institute of Medical Sciences, Wardha, Maharashtra, India.

Tel: +07152284341

Citation: Chhabra S, Singh A (2017) Dangers to Mothers and Babies in Early Onset Hypertensive Disorders. J Women's Health Reprod Med. Vol.1 No.1:5

Abstract

Objective: To know the present status of etiology, pathology and outcome in women with EO and LO HDsP.

Current status-etiopathogy: Women with LO HDsP are believed to be related to maternal constitution. EO HDsP probably has placental origin with interplay between maternal constitution, placental factors, and inappropriate adaptive changes in pregnancy, predominantly involving cardiovascular and inflammatory system. EO are believed to be associated with increased arterial stiffness that extends beyond pregnancy, leading to adverse vascular outcomes, not so in LO HDsP. Studies are being done about relationship to genetic variations, immune system and association between hCG and a variety of thrombophilia disorders.

Feto-maternal outcome: When HDsP are diagnosed before 34 weeks, mothers and clinicians are faced with difficult decision of early delivery of extremely premature infant, with slim chance of survival, may be with major neurological dysfunction, more so when the baby is immature or continue with pregnancy with major risks to mother and even baby, especially in low resource settings. Conservative management may improve fetal outcome, but maternal mortality, morbidity even intra uterine death are real concerns. Most of EO cases present with severe rapidly progressive disease with significantly higher risk of obstetric interventions, with dangers to mother, baby. However LO HDsP can also become dangerous for the mother as well as baby.

Prevention: Role of aspirin, calcium has been documented in prevention of LO HDsP but continues to be surrounded by controversies. Not much is known about the role in relation to differences in EO or LO HDsP. Studies are also being done about supplementation with vitamins C and E. Some have shown benefits, others not so. Low-molecular-weight heparin has also been studied with no effect in onset of EO or severe pre-eclampsia.

Conclusion: There are controversies about many issues about EO/LO cases of HDsP. A lot of research is needed about their etiology, pathology, management, outcome and prevention.

Keywords: Early onset; Late onset; Hypertensive disorders; Effects; Mother; Baby

Received: November 17, 2017; **Accepted:** November 30, 2017; **Published:** December 05, 2017

Introduction

Concept of early onset (EO), late onset (LO) hypertensive disorders of pregnancy (HDsP), as two different forms is being accepted as they seem to have different etiologists, pathogenesis and effects on mother and baby. However there are commonalities and a lot is still not known and research continues. Hypertensive disorders of pregnancy (HDsP) continue to be among the most significant, intriguing, and unsolved problems in obstetrics. Some women develop hypertension during pregnancy much earlier, some late and have variations in the effects also [1-6]. HDsP are angiogenic disorders, probably originating in very early pregnancy [7] and are clinically visible late in pregnancy. Research continues. Though the importance of gestation at obvious hypertension was

reported many years back, as many cases were reported with poor perinatal outcome with early onset (EO) HDsP [8] this has been relooked with division of HDsP into EO, as *de novo* hypertension with or without proteinuria before 34 weeks gestation and late onset, (LO) at completed and after 34 weeks [9-11]. Efforts are being made to elucidate differences in the causes, pathology and outcome of EO and LO HDsP [12-17]. EO and LO HDsP are believed to be different disease entities with overlapping clinical signs. Researchers believe that EO HDsP, with the potential for more serious adverse outcomes for the mother and the baby, should be regarded as different form of HDsP from LO HDsP.

Literature Review

Literature search was done by various search engines like PubMed, Google, Up-to-date, and other search engines to look at studies, reviews, short commentaries to get the desired information as per the objectives and personal experience was added. There were no criteria whatever literature relevant to the objective was available was looked into. Objective to know the present status of knowledge of pathology, etiology and outcome in EO and LO HDsP.

Current status of division, incidence, etiopathology and feto maternal outcome

The concept of EO and LO HDsP is relatively new. It is being widely accepted that these two entities have different etiologies and should be regarded as different forms of the HDsP [18-21]. However there is still inconsistency among the definitions of EO and LO disorders, where the dividing line varies about gestational age between 28 to 37 weeks [22,23]. Earlier divided HDsP, as preterm (before 37 weeks) and term (completed 37 weeks or more). Because of controversies in the definition of EO and LO disorders, International Society for the Study of Hypertension in Pregnancy [24] had a group of researchers for general agreement and 73.0% suggested to define EO HDsP before 3 4weeks of pregnancy, 18.0% suggested 32 weeks and 9.0% suggested 28 weeks. So now a case is considered EO. If HDsP occur before 34 weeks and LO if it occurs $\geq$ 34 weeks.

Incidence

EO HDsP comprise, a small subset of cases of HDsP (5% to 20%), depending on the studies, but are the most severe form of HDsP [25] have reported the overall preeclampsia rate 3.1%, increasing incidence with gestation, EO and LO preeclampsia, 0.38% and 2.72% respectively. Earlier [26] reported a ratio of 32% in the second trimester, 32% between 28 to 36 weeks, and 36% between 37 to 40 weeks [27] reported the ratio of second trimester HDsP 15.3%, [28,29] 24.51% and reported 23.4%. Similarly the study [18] reported a gradual increase with gestation, ratio of 9.40% before 28 weeks, 19.61% between 28-31 weeks, 13.33% between 32-33 weeks, and 57.66% ≥ 34 weeks of gestation. [30,31] reported only 6.3% cases as EOHDsP. Reported cases of as early as 4th month of pregnancy 3.9%, 26.8% in 8th month and 24.7% in 9th month of pregnancy. Though this is not part of this review if one goes with the standard definition, hypertension (blood pressure of 140 mm of Hg or more systolic and 90 mm of Hg or more diastolic) before 20 weeks is considered essential hypertension and not gestational hypertension. However preeclampsia can be superimposed on essential hypertension.

Etiopathology

The first to report the differences between pathogenesis of EO and LO HDsP [7]. In EO, the physiological changes were found to be restricted to the decidual segment alone, absent throughout the entire length of spiral arteries, seen in basal plates of placenta with a defect in the normal interaction between migratory trophoblastic and maternal uterine tissues [32]. After doing review of the literature about epidemiology and pathology supported the hypothesis that preeclampsia was the result of heterogeneous causes [3,17] also reported that, unlike EO preeclampsia, which involved severe placental pathology, LO preeclampsia with intact placenta and maternal cardiovascular deregulation may be prevented with a lifestyle intervention, in particular, low intensity exercise [33] reported that the placenta of women with LO HDsP was similar to placenta of gestational-age-matched normal controls [34], reported that in cases of EO HDsP, endothelial damage was because of abnormal placentation, whereas in LO cases, endothelial damage has been linked to association of insulin resistance(IR). A stronger association with inadequate and incomplete spiral artery remodelling, visualized by alterations in uterine artery Doppler flow has been reported in EO cases, not in LO cases. EO HDsP have been found to be characterized by marked vascular, metabolic and inflammatory changes which were responsible for generalized endothelial dysfunction and end-organ damage due to vascular compromise [35] and hence were potentially life-threatening for the mother and the baby [3,12,28]. It is not certain whether EO HDsP have linkage with cardiovascular dysfunction and lifestyle modification [36] reported that trophoblastic invasion into the placental bed in EO preeclampsia (or) intrauterine growth restriction was limited by increased apoptosis, resulting in narrower spiral arteries [37] reported that chorionic villous vascularization was diminished in cases of EO HDsP, which lead to more of small for gestational age (SGA) babies [38]. And also reported placental hypoplasia significantly associated with histological evidence of placental vascular lesions with the disorder in the early third trimester and concluded that the placenta of women with EO HDsP were significantly different from LO cases [39,40]. Also reported that, for most of the cases of EO HDsP, the root cause was the placentation and placental abnormalities. Reported relatively reduced placental perfusion which leads to inflammation, oxidative stress, and endoplasmic reticulum stress, which converged to modify maternal physiology, endothelium being an important target. Redman and colleagues [3] also reported that EO HDsP were caused by endovascular trophoblastic remodelling, Madazli et al. [41] reported that the magnitude of defective trophoblastic invasion of the spiral arteries correlated with the severity of the disorder [42]. Reported that EO, but not LO HDsP were associated with increased arterial stiffness that extended beyond pregnancy and later contributed to adverse vascular outcome, Yinon et al. [43] reported that women with a history of EO preeclampsia or intrauterine growth restriction without preeclampsia exhibited impaired vascular function,

which might explain their predisposition to placental disease and their higher risk of future vascular disease [14]. Reported that in cases of EOHDsP, placental growth factor was lower and soluble fms like tyrosine kinase-1 and vascular cell adhesion molecule-1 higher than in controls. In LO HDsP, the patients with abnormal uterine artery Doppler indices had higher soluble fms-like tyrosine kinase-1 and vascular cell adhesion molecule-1 levels [40,44,45]. Reported changes of the blood flow within the placental bed spiral arteries and in the uterine arteries at different gestations. In EOHDsP, notches and other changes like increased pulsatility index [PI] of the uterine Doppler waveforms were detected and these women with a persistent abnormal mean PI represented the group with the greatest risk for adverse perinatal outcome. Blair et al. [46]. reported that EO preeclampsia was a severe form of pre-eclampsia that was associated with altered physiological characteristics and gene expression in the placenta. This case control study focused on DNA methylation and gene expression of whole chorionic villi samples from 20 EO HDsP placentas and 20 gestational age matched controls from preterm births and reported that there were wide spread DNA methylation alterations in EOHDsP but not in LO HDsP, which might have been associated with changes in placental function. Masuyama et al. [47] reported the blood levels of adipocytokines differing with a significant elevation of lepton in both subtypes, relative to controls but adiponectin was increased only in LOHDsP. Significant differences in angiogenic factors and adiponectin were found between normal and overweight women only in LOHDsP. Rolfo et al. [48] reported that disruption of oxygen sensing in EO HDsP vs. LO HDsP and control placentae, was the first molecular evidence of the existence of two distinct preeclampsia diseases and the unique molecular O_2 sensing signature of EO-PE placentae may be of diagnostic value when assessing high risk pregnancies and their severity. Probably high levels of interleukin-6 and fibrinogen were associated with a history of EOHDsP [49]. Examined whether allelic variants of the innate immune receptors, Toll-like receptor 4 (TLR4) and nucleotide-binding oligomerization domain 2 (NOD2), (that impair the inflammatory response to endotoxin), were related to preeclampsia and haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and reported an association of common TLR4 and NOD2 gene variants, and pro-inflammatory phenotype with history of EO preeclampsia and HELLP syndrome. Researchers also determined five common mutations in TLR4 (D299G and T399I) and NOD2 (R702W, G908R and L1007fs) in 340 primiparous women with a history of EO preeclampsia, of whom 177 (51%) women had developed HELLP syndrome and 113 women with a history of uneventful pregnancies worked as controls. In addition, researchers assessed plasma levels of pro inflammatory biomarkers C-reactive protein, interleukin-6, soluble intercellular adhesion molecule-1, fibrinogen and von Will ebr factor in a subset of 214 women followed for at least six months after delivery. After adjustment for maternal age and chronic hypertension, attenuating allelic variants of TLR4 were found to be more common in women with a history of EO than in controls (or 2.9 [95% CI 1.2-6.7]). According to genetic factors accounted for more than half the incidence of preeclampsia and maternal genes contributed more than fetal genes, and a couple effect occurred because of the interaction between genes of the mother and the father. Cnattingius et al. and Kovo et al. [50,51] reported that the EO HDsP had higher rates of FGR with lesions of maternal vascular supply compared]. The researchers also concluded that the placental/fetal vascular supply in combination with maternal vascular lesions were more dominant in EO disorders with FGR, compared with EOHDsP without FGR.

Park et al in their study of Australian population for prediction of HDsP have reported that a variety of demographic factors, mean maternal arterial blood pressure (MAP), uterine artery **pulsatility index** (UtA PI) and pregnancy associated plasma protein A (PAPP-A) could predict EO pre-eclampsia in 95% of women with 10% false-positive rate [52].

Feto-maternal outcome

When pre-eclampsia is diagnosed before 34 weeks, clinicians and mothers are faced with difficult decision of either early delivery of an extremely premature infant with a slim chance of survival and major neurological handicap or continue the pregnancy with risk to the woman's health. Most of the EO cases have been reported to be associated with FGR [9,20,21,44,45]. An important cause of preterm birth and adverse maternal and neonatal outcome [28,59] reported larger impact on the foetus and the neonate in EO cases due to more chances of prematurity and immaturity. Paruk et al., Hall et al., Ganzevoort et al. and Ebeigbe et al. [53-57] reported that EOHDsP, by virtue of their unpredictable nature and prediction for multi-organ involvement were associated with substantial maternal and fetal morbidity and mortality. Zhnag et al. and Irgens et al. [57,58] reported unfavourable long-term maternal consequences for women with a history of EO disorder. Sezik et al. and Gasem et al. [59,60] reported 8% to 22% HELLP/ELLP in EO disorders, maybe because more cases were managed conservatively for longer duration. Researchers [24] reported renal failure in 13%, placental abruption in 15%, preterm preeclampsia cases and concluded that a conservative approach to the management of EOHDsP resulted in a good obstetric outcome for the majority of foetuses, but this needed to be balanced against the significant risk of increase in morbidity to the mother. Also, reported a twofold increase in maternal mortality and a significantly increased incidence of renal failure and HELLP syndrome in EO cases. The perinatal mortality was fourfold in the EO cases compared to the LO cases, principally due to prematurity and FGR. Bombrys [61] reported that with expectant management, 36% patients of EO HDsP (at ≤ 32 weeks) had pulmonary edema or haemolytic anaemia. The researchers concluded that there was significant maternal morbidity at ≥ 32 weeks with minimal neonatal benefits and so, early intervention following corticosteroid administration was needed. However, in countries with low resources for neonatal care of very LBW babies, perinatal loss is high, so a balance is essential in a retrospective study of 264 singleton pregnancies with LO HDsP reported that 57.6% were severe and median gestational age at diagnosis was 37 (34-43) weeks, 30.7% of patients experienced ≥ 1 major maternal complication and also 34 (12.9%) cases of eclampsia and there were 5 intrauterine deaths, all due to

placental abruption. The researchers concluded that LO disorders were also not innocuous.

In their studies reported the mean gestational age at delivery in EOHDsP 29 weeks and in LO disorders 37 weeks [62,63]. The researchers concluded that most of the EO cases who presented with severe and rapidly progressive disease were associated with significantly higher risk of obstetric interventions and poorer perinatal outcome, than LOHDP. In a population-based retrospective cohort study, Chang et al. [64] reported that despite a second normotensive pregnancy, women with EO disease in their first pregnancy had greater odds of SGA infants, preterm births, fetal deaths, CS and placental abruption in the second pregnancy, compared to women with LO after controlling for confounders reported cesarean section rate of 58.7% in EOHDsP and significant maternal morbidity. Researchers reported that 84.8% patients of EOHDsP had preterm births. The disease was severe at presentation or rapidly progressive leading to delivery within 72 hours of presentation [31] Ebeigbe et al. reported 19.4% preterm births in cases who had hypertensive disorders at 4th month of pregnancy which dropped to 4% at 9th month [55-58]. In their prospective study reported that a mean of 11 days were gained by expectant management in EOHDsP. The perinatal mortality rate was 24 with a neonatal survival rate of 94%. In a larger retrospective study of 49,812 women, reported that of second trimester HDsP cases, there were 16.9% intrauterine deaths and 12% neonatal deaths. Irgens et al. [58] also reported unfavorable neonatal outcome in women with EOHDsP have reported mean gain of 8.8 ± 1.5 (range 1-19 weeks) weeks in gestational age in the early onset cases Ganzevoort et al. [56] reported that adverse neonatal outcome in EO HDsP was predominantly influenced by gestational age but in the study by Sezik et al. [59] conservative management was associated with 94.5% IUDs. The researchers concluded that in low-resource settings, expectant management of EO HDsP was associated with relatively higher rates of perinatal mortality and should be limited to gestational ages between 28 and 34 weeks of gestation [60]. In their study reported the mean birth weight in EOHDsP 998 ± 323 gms and in LO disorders 2345 ± 479 gms. In their retrospective analysis of outcome in patients with severe preeclampsia, Bombrys et al. [61] reported the birth weights of 27% babies <10% for gestational age, and 8% <5% at 27 to 33 weeks of gestation [62,63].

Prediction of early and late-onset HDsP

Various demographic and other factors have been studied for prediction of EO and LO HDsP, Crispi et al. [64] reported the mean age of women who had EOHDsP 29 ± 5 and LO disorder 32 ± 5 years. However, Valensise et al. [15] reported a mean age of 32 ± 4 years in EO and 34 ± 4 years in LO category. Although an age more than 35 year is linked to a higher risk for preeclampsia, the importance of age in EO and LO has not been studied well. In a retrospective [61] Kennethe et al. reported 56.8% primigravida with LO diseases, Crispi e al. [14] reported 83% primigravida in EO category and 41% in LO, Akolekar et al. [65] reported nulliparous women 58% in EO and 64.2% in LO cases. More research is essential, Kaaja et al. [66] reported that LOHDsP had increased IR, which persisted for around 3 months after pregnancy. Wolf and colleagues [67] reported that the women who had increased IR in the first trimester, were at an increased risk of subsequent preeclampsia in last few weeks (LO) of pregnancy, with the mean gestational age at delivery of 37.6 ± 3 weeks [36] evaluated the first trimester plasma adiponectin mean concentrations in EO HDsP and found a significant difference in adiponectin plasma values only between women in the LO pre-eclampsia group versus those in the control group. First trimester mean homeostasis model assessment ratio values, were significantly higher in the preeclampsia group than that in the control group. In preeclampsia women with standard normal glucose tolerance, an increased IR was associated only with LOHDsP, Pilalis et al. [68] measured the uterine artery blood flow and reported that abnormal uterine Doppler at 11-14 weeks identified one-third of women who were likely to have EO severe pre-eclampsia [69,70] have also reported similar findings compared maternal cardiac function at 24 weeks gestation in a group of normotensive asymptomatic patients with subsequent development of EO and LO and supported the hypothesis of different hemodynamic and origins for EO HDsP [71] evaluated the soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), and sFlt-1 / PlGF ratio for the prediction of EO and LO disorders in a high-risk cohort and reported that serum PlGF concentrations were lower in women who developed disorders early, compared to those who developed LO disorders.

Discussion

Prevention and new research

A study and reported that supplementation with 2 gms of Calcium per day decreased the incidence of HDsP, however information was limited about EO/LO cases [72,73] suggested that in persons with low-calcium diets who were at high risk of hypertensive disorders, calcium supplementation could prevent the development of HDsP but not much was reported about difference between EO and LO. Role of calcium needs more studies. A Meta-analysis of many trials suggested that administration of low dose aspirin at or before the 16th week of pregnancy was associated with a small but significant reduction in the risk for preeclampsia and preterm births. This finding also differed significantly from the later than 16 weeks group. However there is not much information about differences between EO and LO HDsP, Schiff et al. [74,75] reported that daily low dose of aspirin taken during the third trimester of pregnancy significantly reduced the incidence of HDsP in women at high risk for these disorders, possibly through the correction of an imbalance between levels of thromboxane and prostacyclin, but did not comment about EO and LO [76] reported that low dose aspirin and antioxidants may have beneficial effect in the prevention of HDsP in the high risk primigravida subjects, by restoring prostacyclin/thromboxane imbalance, previously suggested as an important aetiological factor in gestational hypertension and preeclampsia but not about relation with EO and LO. Some others have also reported similar findings [77,78]. Study revealed that there were significant differences in fetal and neonatal growth between EO and LO preeclampsia and the

catch up for growth might have started during neonatal period. Studies are being done about the association between a variety of thrombophilia disorders and EO pre-eclampsia [79,80]. Some of these disorders, such as hyperhomocysteinaemia, can easily be corrected from the metabolic point of view [81-83], but currently it is unknown whether or not metabolic correction translated into improved perinatal outcome, Chappell et al. [84] reported the beneficial effects of vitamin C and E on markers of oxidative stress, endothelial activation, and the frequency of EO pre-eclampsia. However studies have shown no reduction in the rates of either serious adverse outcomes of pregnancy associated hypertension or preeclampsia among low risk, nulliparous women. The findings of several studies provided no support for the use of vitamin C and E supplementation in pregnancy to reduce the risk of preeclampsia or its complications [85]. Research continues. From meta-analysis of individual patients, Carbillon et al. [86] reported that low-molecular-weight heparin did not reduce the composite outcome of EO or severe pre -eclampsia, birth of small for gestational age neonates, fetal loss, or placental abruption and in subgroup analyses, did not reduce the risk of EO pre-eclampsia.

Future of Women with EO LO HDsP

Those women who had EOHDsP had higher risk of developing cardiovascular morbidity at middle age. Irgens et al. [58] did a large follow-up study and provided evidence of increased risk of dying because of cardiovascular disease after EO and a lower risk after LO preeclampsia. This raised the question whether this effect was secondary to the acquired metabolic syndrome during pregnancy in these women or to an inherited accelerated aging of the cardiovascular system [86-89]. Earlier studied 125 women with severe preeclampsia in the second trimester with follow-up for an average of 5.4 years and reported increased risk for repeat preeclampsia, particularly the second trimester cases. They were at higher risk of morbidity and mortality in subsequent pregnancies also and chronic hypertension. Others also reported that women who get EO HDsP have more chances of recurrence in future pregnancy with risk for a variety of cardiovascular disorders (CVD) like stroke, coronary artery disease, heart failure, and peripheral vascular disease [90]. Researchers reported differences in the prevalence of common modifiable CVD risk factors postpartum and suggested that prevention strategies should be stratified according to severity and gestational age at onset of the HDsP [90,91].

Conclusion

EO and LO HDsP seem to be disorders with different etiology, different pathology different feta maternal outcome and different squeal, with some commonalities in all the aspects. There are dangerous outcomes in both, but more serious in EO. Both continue to create serious problems for mother and baby. A lot of more research is needed.

References

1 Viniker D, Chattopadhyay B (2000) Antioxidants and pre-eclampsia. Lancet 355: 65-66.

2 Walker JJ (2000) Pre-eclampsia. Lancet 356: 1260-1265.

3 Redman CW, Sargent IL (2005) Latest advances in understanding preeclampsia. Science 308: 1592-1594.

4 Hutcheon JA, Lisonkova S, Joseph KS (2011) Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol 25: 391-403.

5 Backes CH, Markham K, Moorhead P, Cordero L, Nankervis CA, et al. (2011) Maternal preeclampsia and neonatal outcomes. J Pregnancy 2011: 214-365.

6 Alves E, Azevedo A, Rodrigues T, Santos AC, Barros H (2013) Impact of risk factors on hypertensive disorders in pregnancy, in primiparae and multipara. Ann Hum Biol 40: 377-384.

7 Khong TY, De Wolf F, Robertson WB, Brosens I (1986) Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. Br J Obstet Gynaecol 93: 1049-1059.

8 Pijnenborg R, Anthony J, Davey DA, Tiltman A, Vercruysse L, et al. (1991) Placental bed spiral arteries in the hypertensive disorders of pregnancy. Br J Obstet Gynaecol 98: 648-655.

9 Moore MP, Redman CW (1983) Case-control study of severe pre-eclampsia of early onset. Br Med J (Clin Res Ed) 287: 580-583.

10 Von Dadelszen P, Magee LA, Roberts JM (2003) Sub classification of preeclampsia. Hypertens pregnancy 22: 143-148.

11 Roberts JM, Bell MJ (2013) If we know so much about preeclampsia, why haven't we cured the disease? J Reprod Immunol 99: 1-9.

12 Sibai B, Dekker G, Kupferminc M (2005) Pre-eclampsia. Lancet 365: 785-799.

13 Vatten LJ, Skjaerven R (2004) Is pre-eclampsia more than one disease? BJOG 111: 298-302.

14 Crispi F, Dominguez C, Llurba E, Martin-Gallan P, Cabero L, et al. (2006) Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction. Am J Obstet Gynecol 195: 201-207.

15 Valensise H, Vasapollo B, Gagliardi G, Novelli GP (2008) Early and late preeclampsia: Two different maternal hemodynamic states in the latent phase of the disease. Hypertension 52: 873-880.

16 Raymond D, Peterson E (2011) A critical review of early-onset and late-onset preeclampsia. Obstet Gynecol Surv 66: 497-506.

17 Yeo S (2011) A risk reduction model for late-onset preeclampsia: A theory for using low-intensity exercises to enhance cardiac homeostasis in nursing research and practice. ANS Adv Nurs Sci 34: 78-88.

18 Junus K, Centlow M, Wikstrom AK, Larsson I, Hansson SR, et al. (2012) Gene expression profiling of placentae from women with early- and late-onset pre-eclampsia: Down-regulation of the angiogenesis-related genes ACVRL1 and EGFL7 in early-onset disease. Mol Hum Reprod 18: 146-55.

19 Yang Z, Li R, Shi LY, Wang LN, Ye RH, et al. (2005) Clinical delimitation and expectant management of early onset of severe pre-eclampsia. Zhonghua Fu Chan Ke Za Zhi 40: 302-305.

20 Yang Z, Wang JL, Huang P, Shi LY, Li R, et al. (2006) Study on different onset patterns and perinatal outcomes in severe preeclampsia. Zhonghua Fu Chan Ke Za Zhi 41: 302-306.

21 Huppertz B (2008) Placental origins of preeclampsia: Challenging the current hypothesis. Hypertension 51: 970-975.

22 Kang A, Struben H (2008) Pre-eclampsia screening in first and second trimester. Ther Umsch 65: 663-666.

23 Murphy DJ, Stirrat GM (2000) Mortality and morbidity associated with early-onset preeclampsia. Hypertens Pregnancy 19: 221-231.

24 Steegers EA, Von Dadelszen P, Duvekot JJ, Pijnenborg R (2010) Pre-eclampsia. Lancet 376: 631-644.

25 Tranquillie AL, Brown MA, Zeeman GG, Dekker G, Sibai BM (2013) The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 3: 44-47.

26 Lisonkova S, Joseph KS (2013) Incidence of preeclampsia: Risk factors and outcomes associated with early- versus late-onset disease. Am J Obstet Gynecol 209: 544-545.

27 Sibai BM, Mercer B, Sarinoglu C (1991) Severe preeclampsia in the second trimester: Recurrence risk and long-term prognosis. Am J Obstet Gynecol 165: 1408-1412.

28 Meis PJ, Goldenberg RL, Mercer BM, Iams JD, Moawad AH, et al. (1998) The preterm prediction study: Risk factors for indicated preterm births. Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development. Am J Obstet Gynecol 178: 562-7.

29 Shenhav S, Gemer O, Sassoon E, Volodarsky M, Peled R, et al. (2002) Mid-trimester triple test levels in early and late onset severe pre-eclampsia. Prenat Diagn 22: 579-82.

30 Onah HE, Iloabachie GC (2002) Conservative management of early-onset pre-eclampsia and fetomaternal outcome in Nigerians. J Obstet Gynaecol 22: 357-362.

31 Ebeigbe PN, Aziken ME (2010) Early onset pregnancy-induced hypertension/eclampsia in Benin City, Nigeria. Niger J Clin Pract 13: 388-393.

32 Banhidy F, Dakhlaoui A, Dudas I, Czeizel AE (2011) Birth outcomes of newborns after folic Acid supplementation in pregnant women with early and late pre-eclampsia: A population-based study. Adv Prev Med 127369.

33 Ness RB, Roberts JM (1996) Heterogeneous causes constituting the single syndrome of preeclampsia: A hypothesis and its implications. Am J Obstet Gynecol 175: 1365-1370.

34 Egbor M, Ansari T, Morris N, Green CJ, Sibbons PD (2006) Morphometric placental villous and vascular abnormalities in early- and late-onset pre-eclampsia with and without fetal growth restriction. BJOG 113: 580-589.

35 Danna R, Baviera G, Corrado F, Giordano D, De Vivo A, et al. (2006) Adiponectin and insulin resistance in early-and late-onset pre-eclampsia. BJOG 113: 1264-1269.

36 Redman CW, Sargent IL (2003) Pre-eclampsia, the placenta and the maternal systemic inflammatory response-a review. Placenta 24: S21-S27.

37 Kadyrov M, Kingdom JC, Huppertz B (2006) Divergent trophoblast invasion and apoptosis in placental bed spiral arteries from pregnancies complicated by maternal anemia and early-onset preeclampsia/intrauterine growth restriction. Am J Obstet Gynecol 194: 557-563.

38 Van Oppenraaij RH, Bergen NE, Duvekot JJ, De Krijger RR, Steegers EA, et al. (2011) Placental vascularization in early onset small for gestational age and preeclampsia. Reprod Sci 18: 586-593.

39 Nelson DB, Ziadie MS, Mcintire DD, Rogers BB, Leveno KJ (2014) Placental pathology suggesting that preeclampsia is more than one disease. Am J Obstet Gynecol 210: 1-7

40 Carbillon L, Challier JC, Alouini S, Uzan M, Uzan S (2001) Uteroplacental circulation development: Doppler assessment and clinical importance. Placenta 22: 795-799.

41 Madazli R, Budak E, Calay Z, Aksu MF (2000) Correlation between placental bed biopsy findings, vascular cell adhesion molecule and fibronectin levels in pre-eclampsia. BJOG 107: 514-518.

42 Khalil A, Jauniaux E, Harrington K (2009) Antihypertensive therapy and central hemodynamics in women with hypertensive disorders in pregnancy. Obstet Gynecol 113: 646-654.

43 Yinon Y, Kingdom JC, Odutayo A, Moineddin R, Drewlo S, et al. (2010) Vascular dysfunction in women with a history of preeclampsia and intrauterine growth restriction: Insights into future vascular risk. Circulation 122: 1846-1853.

44 Aardema MW, Oosterhof H, Timmer A, Van Rooy I, Aarnoudse JG (2001) Doppler flow and uteroplacental vascular pathology in normal pregnancies and pregnancies complicated by pre-eclampsia and small for gestational age fetuses. Placenta 22: 405-411.

45 Gomez O, Figueras F, Martinez JM, Del Rio M, Palacio M, et al. (2006) Sequential changes in uterine artery blood flow pattern between the first and second trimesters of gestation in relation to pregnancy outcome. Ultrasound Obstet Gynecol 28: 802-808.

46 Blair JD, Yuen RK, Lim BK, Mcfadden DE, Von Dadelszen P, et al. (2013) Widespread DNA hypomethylation at gene enhancer regions in placentas associated With Early-Onset Pre-Eclampsia. Mol Hum Reprod 19: 697-708.

47 Masuyama H, Segawa T, Sumida Y, Masumoto A, Inoue S, et al. (2010) Different profiles of circulating angiogenic factors and adipocytokines between early- and late-onset pre-eclampsia. BJOG 117: 314-320.

48 Rolfo A, Many A, Racano A, Tal R, Tagliaferro A, et al. (2010) Abnormalities in oxygen sensing defines early and late onset preeclampsia as distinct pathologies. PLoS One 5: e13288.

49 Van Rijn BB, Franx A, Steegers EA, De Groot CJ, Bertina RM, et al. (2008) Maternal TLR4 and NOD2 gene variants, pro-inflammatory phenotype and susceptibility to early-onset preeclampsia and HELLP syndrome. PLoS One 3: e1865.s

50 Cnattingius S, Reilly M, Pawitan Y, Lichtenstein P (2004) Maternal and fetal genetic factors account for most of familial aggregation of pre-eclampsia: A population-based Swedish cohort study. Am J Med Genet A 130: 365-371.

51 Kovo M, Schreiber L, Ben-Haroush A, Gold E, Golan A, et al. (2012) The placental component in early-onset and late-onset preeclampsia in relation to fetal growth restriction. Prenat Diagn 32: 632-637.

52 Park FJ, Leung CH, Poon LC, Williams PF, Rothwell SJ, et al. (2013) Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy. Aust N Z J Obstet Gynaecol 53: 532-539.

53 Paruk F, Moodley J (2000) Maternal and neonatal outcome in early- and late-onset pre-eclampsia. Semin Neonatol 5: 197-207.

54 Hall DR, Odendaal HJ, Kirsten GF, Smith J, Grove D (2000) Expectant management of early onset, severe pre-eclampsia: perinatal outcome. BJOG 107: 1258-1264.

55 Ganzevoort W, Rep A, De Vries JI, Bonsel GJ, Wolf H (2006) Prediction of maternal complications and adverse infant outcome at admission for temporizing management of early-onset severe hypertensive disorders of pregnancy. Am J Obstet Gynecol 195: 495-503.

56 Kimura C, Watanabe K, Iwasaki A, Mori T, Matsushita H, et al. (2013) The severity of hypoxic changes and oxidative DNA damage in the placenta of early-onset preeclamptic women and fetal growth restriction. J Matern Fetal Neonatal Med 26: 491-496.

57 Zhang H, Zhang Y, Yang F, Li L, Liu S, et al. (2011) Complement component C4A and apolipoprotein A-I in plasmas as biomarkers of the severe, early-onset preeclampsia. Mol Biosyst 7: 2470-2479.

58 Irgens HU, Reisaeter L, Irgens LM, Lie RT (2001) Long term mortality of mothers and fathers after pre-eclampsia: Population based cohort study. BMJ 323: 1213-1217.

59 Sezik M, Ozkaya O, Sezik HT, Yapar EG (2007) Expectant management of severe preeclampsia presenting before 25 weeks of gestation. Med Sci Monit 13: CR523-527.

60 Gasem T, Al Jama FE, Burshaid S, Rahman J, Al Suleiman SA, et al. (2009) Maternal and fetal outcome of pregnancy complicated by HELLP syndrome. J Matern Fetal Neonatal Med 22: 1140-1143.

61 Bombrys AE, Barton JR, Habli M, Sibai BM (2009) Expectant management of severe preeclampsia at 27(0/7) to 33(6/7) weeks' gestation: Maternal and perinatal outcomes according to gestational age by weeks at onset of expectant management. Am J Perinatol 26: 441-446.

62 Kenneth L, Hall DR, Gebhardt S, Grove D (2010) Late onset preeclampsia is not an innocuous condition. Hypertens Pregnancy 29: 262-270.

63 Crispi F, Llurba E, Dominguez C, Martin-Gallan P, Cabero L, et al. (2008) Predictive value of angiogenic factors and uterine artery Doppler for early- versus late-onset pre-eclampsia and intrauterine growth restriction. Ultrasound Obstet Gynecol 31: 303-309.

64 Chang JJ, Muglia LJ, Macones GA (2010) Association of early-onset pre-eclampsia in first pregnancy with normotensive second pregnancy outcomes: A population-based study. BJOG 117: 946-953.

65 Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH (2011) Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. Prenat Diagn 31: 66-74.

66 Kaaja R, Laivuori H, Laakso M, Tikkanen MJ, Ylikorkala O (1999) Evidence of a state of increased insulin resistance in preeclampsia. Metabolism 48: 892-896.

67 Wolf M, Sandler L, Munoz K, Hsu K, Ecker JL, et al. (2002) First trimester insulin resistance and subsequent preeclampsia: A prospective study. J Clin Endocrinol Metab 87: 1563-1568.

68 Pilalis A, Souka AP, Antsaklis P, Basayiannis K, Benardis P, et al. (2007) Screening for pre-eclampsia and small for gestational age fetuses at the 11-14 weeks scan by uterine artery Dopplers. Acta Obstet Gynecol Scand 86: 530-534.

69 Ferrazzi E, Rigano S, Padoan A, Boito S, Pennati G, et al. (2011) Uterine artery blood flow volume in pregnant women with an abnormal pulsatility index of the uterine arteries delivering normal or intrauterine growth restricted newborns. 32: 487-492.

70 Browne VA, Julian CG, Jaldin LT, Ragan DC, Vegas E, et al. (2015) Uterine artery blood flow, fetal hypoxia and fetal growth. Philos Trans R Soc Lond B Biol Sci 5: 1663.

71 Villa PM, Hamalainen E, Maki A, Raikkonen K, Pesonen AK, et al. (2013) Vasoactive agents for the prediction of early- and late-onset preeclampsia in a high-risk cohort. BMC Pregnancy Childbirth 13: 110.

72 Jose MB, Jose V, Gonzalez RN, Campodonico L, Bergel E (1991) Calcium supplementation to prevent hypertensive disorders of pregnancy. N Engl J Med 325:1399-1405.

73 Stringer JD (2015) Calcium supplementation for preventing hypertensive disorders in pregnancy. 1: 570-571.

74 Brooke L, Bujold E (2013) Aspirin in Pregnancy: Beyond Preeclampsia. Medscape.

75 Schiff E, Peleg E, Goldenberg M, Rosenthal T, Ruppin E, et al. (1989) The use of aspirin to prevent pregnancy-induced hypertension and lower the ratio of thromboxane A2 to prostcyclin in relatively high risk pregnancies. N Engl J Med 321: 351-356.

76 http://www.ssjournals.com/index.php/ijbar/article/view/1428

77 Rolnik DL, Wright D, Poon LC, Gorman NO, Syngelaki A, et al. (2017) Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 377: 613-622.

78 Mitsui T, Masuyama H, Nobumoto E, Hayata K, Hiramatsu Y (2015) Different fetal and neonatal growth between early and late onset preeclampsia. Open J Obstet Gynecol 5: 516-521.

79 Czeizel AE, Puho EH, Langmar Z, Acs N, Banhidy F (2010) Possible association of folic acid supplementation during pregnancy with reduction of preterm birth: a population-based study. Eur J Obstet Gynecol Reprod Biol 148: 135-140.

80 Pandey K, Dubay P, Bhagoliwal A, Gupta N, Tyagi G (2012) Hyperhomocysteinemia as a risk factor for IUGR. J Obstet Gynaecol 62: 406-408.

81 Leeda M, Riyazi N, De Vries JI, Jakobs C, Van Geijn HP (1998) Effects of folic acid and vitamin B6 supplementation on women with hyperhomocysteinemia and a history of preeclampsia or fetal growth restriction. Am J Obstet Gynecol 179: 135-139.

82 Mignini LE, Latthe PM, Villar J, Kilby MD, Carroli G, et al. (2005) Mapping the theories of preeclampsia: The role of homocysteine. Obstet Gynecol 105: 411-425.

83 Barton JR, Sibai BM (2008) Prediction and prevention of recurrent preeclampsia. Obstet Gynecol 112: 359-372.

84 Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, et al. (1999) Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: A randomised trial. Lancet 354: 810-816.

85 Roberts JM, Myatt L, Spong CY, Thom EA, Hauth JC, et al (2010) Vitamins C and E to prevent complications of pregnancy-associated hypertension. N Engl J Med 8: 1282-1291.

86 Carbillon L (2017) Prevention of early-onset pre-eclampsia. Lancet 389:1514–1515.

87 Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA (2005) Cardiovascular health after maternal placental syndromes (CHAMPS): Population-based retrospective cohort study. Lancet 366: 1797-803.

88 Wikstrom AK, Haglund B, Olovsson M, Lindeberg SN (2005) The risk of maternal ischaemic heart disease after gestational hypertensive disease. BJOG 112: 1486-1491.

89 Skjaerven R, Wilcox AJ, Klungsoyr K, Irgens LM, Vikse BE, et al. (2012) Cardiovascular mortality after pre-eclampsia in one child mothers: Prospective, population based cohort study. BMJ 345: e7677.

90 Veerbeek JH, Hermes W, Breimer A, Van Rijn B, Koenen SV, et al. (2015) Cardiovascular disease risk factors after early-onset preeclampsia, late-onset preeclampsia, and pregnancy- induced. Hypertension 65: 600-606.

91 Valdiviezo C, Garovic VD, Ouyang P (2012) Preeclampsia and hypertensive disease in pregnancy: Their contributions to cardiovascular risk. Clin Cardiol 35:160-165.