Journal of Infertility and Reproductive Biology

J Infertil Reprod Biol, 2017, Volume 5, Issue 4, Pages: 20-25. https://doi.org/10.47277/JIRB/5(4)/20

# Maternal, Fetal and Placental Responses in the Early and Late Onset Preeclampsia

**Mona Sharma[1*], Renu Dhingra[2], Neerja Bhatla[3]**

[1] Assistant Professor, Department of Reproductive Biology, All India Institute of Medical Sciences, New Delhi, India
[2] Professor, Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India
[3] Professor, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi, India

Received: 17/09/2017 Accepted: 20/11/2017 Published: 20/12/2017

## Abstract

Preeclampsia is the pregnancy induced disorder of hypertension and proteinuria manifesting after midgestation. Depending upon the onset of symptoms, it can be classified as early onset (≤34 wks) or late onset (≥34wks). The objectives of the present study were to compare the maternal responses (maternal age, gestational age, mode of delivery, blood pressure, proteinuria), the fetal responses (birth weight, APGAR score) and placental responses (placental weight, placental morphology, trophoblastic and syncytial knot apoptotic rates) between the early and late onset preeclamptic women. The study group included early onset (20 placentas), late onset (20 placentas) cases of preeclampsia and control group included 20 placentas from normotensive nonproteinuric pregnant women. For the placental pathological changes, hematoxylin and eosin staining and M30 immunostaining were used. The maternal, fetal and placental responses were compared between study and control groups. As compared to the control group, the maternal age, blood pressure and proteinuria were higher in both early and late onset preeclamptic groups. The early onset preeclamptic group was associated with low placental weight along with premature delivery of low birth weight babies with low APGAR scores as compared to control and late onset preeclamptic group. The mode of delivery in most of the cases of early onset preeclamptic group was caesarean section. The fetal and placental responses in late preeclamptic group were comparable to that of control group. The placental villous and vascular morphology along with apoptotic indices were severely altered in early onset preeclamptic group. Between the two types of preeclampsia, the early onset preeclamptic group showed poor maternal, fetal and placental responses suggesting its severity and bad prognosis.

**Keywords**: Preeclampsia, Maternal age, Placentas, Premature delivery, APGAR Score

## Introduction

The pregnancy associated hypertensive disorders are one of the causes of maternal mortality all over the world. A thorough understanding of the current causes of maternal mortality is crucial for addressing the challenge of high rates of maternal mortality. The International Society for the study of Hypertension in Pregnancy (ISSHP) defines preeclampsia as the onset of sudden hypertension (systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90 mmHg) along with proteinuria ≥300 mg in a 24-hour collection of urine after 20$^{th}$ weeks of gestation in a previously normotensive, nonproteinuric pregnant woman. These identifying clinical features should disappear by the end of third month postpartum (1).

The pathological features of this disorder have been correlated with the aberrant trophoblastic life cycle. The exaggerated rate of trophoblastic apoptosis in preeclamptic placentas leads to insufficient trophoblastic invasion causing abnormal implantation and placental vascular insufficiency (2). Apoptosis is the natural mechanism of trophoblast turnover process and it involves extrinsic and intrinsic mechanisms (3). Placental trophoblastic cells form abundant syncytial knots which get detach from the villous surface into maternal circulation (4). These syncytial aggregates stimulate the maternal immune system and contributes to maternal vascular injury and endothelial dysfunction which centralises the pathogenetic events of this disorder (5). It can be assumed that maternal inflammatory response is the final pathway of this disorder but its initiative routes can vary greatly. Though the hypothesis pertaining to pathological changes of preeclampsia revolves around the abnormal trophoblastic apoptosis and syncytial shedding but the onset of symptoms in preeclampsia greatly differ. In early onset preeclampsia, the symptoms appear at ≤34 wks whereas in late onset preeclampsia, the symptoms appear at ≥34wks of gestation (6). The trophoblastic apoptosis can be estimated by using various cytoplasmic and nuclear apoptotic markers such as annexin v staining, TUNEL, M30 immunostaining. M30 antibody has been used to identify apoptotic changes specifically in the cytoplasm. This antibody identifies the cytokeratin breakdown occurring during apoptosis cascade and it has been used as apoptotic markers for trophoblastic cells (7, 8).

Preeclampsia remains the target of extensive research in recent years and more work needs to be conducted to unfold the underlying pathological events of the subsets of this disorder. Therefore, to circumvent the differences in the onset of cardinal symptoms, we hypothesise that the maternal, fetal and

***Corresponding author:** Mona Sharma, Department of Reproductive Biology, 2 Floor, Teaching Block, AIIMS, New Delhi, India. E-mail: dr.mona18sharma@gmail.com

J Infertil Reprod Biol, 2017, Volume 5, Issue 4, Pages: 20-25. https://doi.org/10.47277/JIRB/5(4)/20

placental responses may differ in the early and late onset preeclampsia.

## Methods

A total of 60 placentas were collected from the labour room of Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi. The ethical committee approved the protocol of the study. The consent was taken from each individual for the study groups. Out of the total samples, 20 placentas were from early onset preeclamptic pregnant women, 20 placentas were from late onset preeclamptic pregnant women and 20 placentas were taken from normotensive nonproteinuric pregnant women. Preeclampsia was diagnosed according to the ISSHP criteria. Patients with chronic hypertension, pregestational diabetes, chorioamnionitis, renal disease, cardiac disease, thyroid disease, pre-existing seizure disorder and HELLP syndrome were excluded from this study.

The placental samples were collected immediately after delivery. The central part of the placental disc was chosen for taking the samples. The areas of visible infarcts, hematomas or calcification were excluded. The placental tissue samples were fixed in 10% formaldehyde and subsequently paraffin blocks and 5µm tissue sections were prepared. Subsequently, tissue sections were deparaffinised rehydrated and processed for hematoxylin and eosin staining and were examined under light microscope. Standard procedure for immunostaining was followed according to manufacturer's protocol. For M30 immunostaining (Roche Diagnostic, Germany), the subsequent steps were carried out at room temperature in a humidified chamber. The 3% $H_2O_2$ prepared in methanol was used for 10 minutes to block peroxidase activity. The specimens were then incubated in 1-3 drops of serum block for 2 hours to prevent non-specific binding to collagen and connective tissue. Further, the specimens were incubated for 24 hrs with M30 antibody (1:50) followed by 1-3 drops of biotinylated secondary antibody (anti mouse IgG) for 30 minutes. Thereafter, the specimens were incubated in 1-3 drops of HRP-streptavidin complex for 30 minutes. The slides were then counterstained with hematoxylin and dehydrated by passing through ascending grades of ethanol. The slides were then mounted with DPX and were observed under light microscope. The negative tissue control included eliminating the primary antiserum and replacing species-specific antiserum with normal horse serum. Sections of colon adenocarcinoma were taken as positive controls. Stained sections showing trophoblastic cells and syncytial knots with the brown cytoplasmic stain were considered M30 immunostaining positive apoptotic cells. The trophoblastic and syncytial knot apoptotic indices were calculated (total number of apoptotic cells per total number of cells multiply by 100). The maternal responses (maternal age, gestational age, mode of delivery, blood pressure, urinary protein), fetal responses (birth weight, APGAR scores) and placental responses (placental weight, placental morphology by hematoxylin and eosin staining, trophoblastic and syncytial knot indices by M30 immunostaining) were compared among the study groups. Statistical analysis was done using Stata 9.0/Data analysis software (college station, Texas). Data were presented as in Mean ±SD (range). For comparison among the study groups, one way ANOVA test with bonferroni correction was applied. P value <0.05 was considered statistically significant. For multiple comparisons, fischer's exact test was used with bonferroni correction and P <0.018 was considered statistically significant.

## Results

### *Maternal Responses*

The systolic blood pressure (SBP) [160±4.6(150-170)] as well as diastolic blood pressure (DBP) [108±6.5(100-118)] were more in early onset preeclamptic group as well as in late onset group [SBP-144±4.4(138-156), DBP-93.9±3.8(90-100) as compared to control group[SBP-112±8.6(100-124), DBP-79.7±6.1(70-90)]. The rate of proteinuria was also more in early onset preeclamptic group [4.1±0.6(3-5)] as well as in late onset preeclamptic group [1.7±0.6(1-2.9)] as compared to the control group [0.16±0.04(0.1-0.2)]. Maternal age was more in early [35±1.9(32-38)] as well as in late onset preeclamptic groups [34.2±2.2(30-38)] as compared to control group [27.6±3.6(20-34)]. The early onset preeclamptic group showed less gestational age [33.6±1.5(31-36)] as compared to the late onset preeclamptic group [37.7±1.2(36-40)] and control group [38.2±1.4(36-41)]. In the early onset preeclamptic group, 90% women were delivered by caesarean sections as compared to late onset preeclamptic (25%) and control group (10%). Amongst the two preeclamptic groups, the early onset group showed higher SBP, DBP and rate of proteinuria (Tables 1-3, 6, 7).

### *Fetal Responses*

The newborns in the early onset group were low weight [2088±166(1800-2400)] as compared to late onset preeclamptic group [2825±226(2500-3500)] and control group [2924±260(2500-3500)]. The newborns delivered from early onset preeclamptic women, 85% of them showed low APGAR scores as compared to late onset preeclamptic (25%) and control group (0%) (Tables 2, 4, 6, 7).

### *Placental Responses*

The placental weight in early onset preeclamptic group was less [376.5±67.7(240-490)] as compared to the late onset preeclamptic [504±50.5(400-600)] and control groups [524±45(440-630)].The early onset preeclamptic placentas showed gross areas of infarcts, hematomas and thrombi. On histological examination, the placental villi showed altered morphological patterns along with interstitial edema. These villi were of variable sizes and were lined by syncytiotrophoblastic cells and less of cytotrophoblastic cells. The villous core composed of mesenchyme and blood vessels. There was increased capillarisation seen in these villi which made their surface deformed. The intervillous space was more in these placentas. The fibrin deposits were seen on the trophoblastic surface. The nuclei of trophoblastic cells aggregated and formed excessive of syncytial knots (figures 1-5). The trophoblastic apoptotic index was more in these group of placentas [91.3±6.3(80-99)] as compared to late onset preeclamptic [62.3±13.8(38-85)] and control groups [ 61.9±14.4(37.3-87.9)]. The syncytial knot apoptotic index was also more in early onset preeclamptic group [87.7±10.1(70-100)] as compared to late onset preeclamptic [43±16.2(10-70)] and control groups [36.9±20.2(0-66.6)]. There were no

J Infertil Reprod Biol, 2017, Volume 5, Issue 4, Pages: 20-25. https://doi.org/10.47277/JIRB/5(4)/20

significant pathological changes observed in the placentas of late onset preeclamptic group (Tables 2, 5-7).

**Table 1: Comparison of Maternal responses in the study groups**

| Parameters | Early Onset Preeclampsia (n= 20) | Late Onset Preeclampsia (n=20) | P value |
|---|---|---|---|
| **Systolic BP (mm Hg)** | 160±4.6(150-170) | 144±4.4(138-156) | <0.0001 |
| **Diastolic BP (mm Hg)** | 108±6.5(100-118) | 93.9±3.8(90-100) | <0.0001 |
| **Proteinuria (g/day)** | 4.1±0.6(3-5) | 1.7±0.6(1-2.9) | <0.0001 |

n = number of subjects, Data is presented in Mean ±SD (range), One way ANOVA test with bonferroni correction; P<0.05, statistically significant

**Table 2: Comparison of Maternal and fetal responses in the study groups**

| Parameters | Early Onset Preeclampsia (n= 20) | Late Onset Preeclampsia (n=20) | P value |
|---|---|---|---|
| **Maternal Age (yrs)** | 35±1.9(32-38) | 34.2±2.2(30-38) | 0.9 |
| **Gestational Age (wks)** | 33.6±1.5(31-36) | 37.7±1.2(36-40) | <0.0001 |
| **Birth Wt (gms)** | 2088±166(1800-2400) | 2825±226(2500-3500) | <0.0001 |
| **Placental Wt (gms)** | 376.5±67.7(240-490) | 504±50.5(400-600) | <0.0001 |

n = number of subjects, Data is presented in Mean ±SD (range), One way ANOVA test with bonferroni correction; P<0.05, statistically significant

**Table 3: Comparison of Maternal parameters (mode of delivery) in study groups**

| Study groups | Percentage | Overall p-value | Multiple comparison (p value <0.018) | | |
|---|---|---|---|---|---|
| | | | Gp 1 Vs Gp 2 | Gp 1 Vs Gp 3 | Gp 2 Vs Gp 3 |
| **Control Group Gp1** | NV-18(90) CS-2(10) | <0.0001 | <0.0001 | 0.407 | <0.0001 |
| **Early Onset PE Gp2** | NV-2(10) CS-18(90) | | | | |
| **Late Onset PE Gp3** | NV-15(75) CS-5(25) | | | | |

Fischer's exact test, statistical significance: P<0.05;

Multiple comparison with bonferroni correction, statistical significance: P<0.018 (NV: normal vaginal delivery; CS: caesarean section)

**Table 4: Comparison of Fetal parameters (APGAR score) in study groups**

| Study Groups | Percentage | Overall p-value | Multiple comparison (p value <0.018) | | |
|---|---|---|---|---|---|
| | | | Gp 1 Vs Gp 2 | Gp 1 Vs Gp 3 | Gp 2 Vs Gp 3 |
| **Control Group Gp1** | ≤7-0(0) ≥7-20(100) | <0.0001 | <0.0001 | 0.047 | <0.0001 |
| **Early Onset PE Gp2** | ≤7-17(85) ≥7-3(15) | | | | |
| **Late Onset PE Gp3** | ≤7-5(25) ≥7-15(75) | | | | |

Fischer's exact test, statistical significance: P<0.05

Multiple comparison with bonferroni correction, statistical significance : P< 0.018

**Table 5: Comparison of Placental responses in the study groups**

| Parameters | Early Onset Preeclampsia (n= 20) | Late Onset Preeclampsia (n=20) | P value |
|---|---|---|---|
| **Trophoblastic Index (%)** | 91.3±6.3(80-99) | 62.3±13.8(38-85) | <0.0001 |
| **Syncytial Knot Index (%)** | 87.7±10.1(70-100) | 43±16.2(10-70) | <0.0001 |

n = number of subjects, Data is presented in Mean ±SD (range), One way ANOVA test with bonferroni correction; P<0.05, statistically significant

Journal of Infertility and Reproductive Biology

J Infertil Reprod Biol, 2017, Volume 5, Issue 4, Pages: 20-25. https://doi.org/10.47277/JIRB/5(4)/20

**Table 6: Comparison of Maternal, fetal and placental parameters in early onset preeclampsia and controls**

| Parameters | Early Onset Preeclampsia (n= 20) | Control (n=20) | P value |
|---|---|---|---|
| **Systolic BP (mm Hg)** | 160±4.6(150-170) | 112±8.6(100-124) | <0.0001 |
| **Diastolic BP (mm Hg)** | 108±6.5(100-118) | 79.7±6.1(70-90) | <0.0001 |
| **Proteinuria (g/day)** | 4.1±0.6(3-5) | 0.16±0.04(0.1-0.2) | <0.0001 |
| **Maternal Age (yrs)** | 35±1.9(32-38) | 27.6±3.6(20-34) | <0.0001 |
| **Gestational Age (wks)** | 33.6±1.5(31-36) | 38.2±1.4(36-41) | <0.0001 |
| **Birth Wt (gms)** | 2088±166(1800-2400) | 2924±260(2500-3500) | <0.0001 |
| **Placental Wt (gms)** | 376.5±67.7(240-490) | 524±45(440-630) | <0.0001 |
| **Trophoblastic Index (%)** | 91.3±6.3(80-99) | 61.9±14.4(37.3-87.9) | <0.0001 |
| **Syncytial Knot Index (%)** | 87.7±10.1(70-100) | 36.9±20.2(0-66.6) | <0.0001 |

n = number of subjects, Data is presented in Mean ±SD (range), One way ANOVA test with bonferroni correction; P<0.05, statistically significant

**Table 7: Comparison of Maternal, fetal and placental parameters in late onset preeclampsia and controls**

| Parameters | Late Onset Preeclampsia (n= 20) | Control (n=20) | P value |
|---|---|---|---|
| **Systolic BP (mm Hg)** | 144±4.4(138-156) | 112±8.6(100-124) | <0.0001 |
| **Diastolic BP (mm Hg)** | 93.9±3.8(90-100) | 79.7±6.1(70-90) | <0.0001 |
| **Proteinuria (g/day)** | 1.7±0.6(1-2.9) | 0.16±0.04(0.1-0.2) | <0.0001 |
| **Maternal Age (yrs)** | 34.2±2.2(30-38) | 27.6±3.6(20-34) | <0.0001 |
| **Gestational Age (wks)** | 37.7±1.2(36-40) | 38.2±1.4(36-41) | 0.6 |
| **Birth Wt (gms)** | 2825±226(2500-3500) | 2924±260(2500-3500) | 0.4 |
| **Placental Wt (gms)** | 504±50.5(400-600) | 524±45(440-630) | 0.8 |
| **Trophoblastic Index (%)** | 62.3±13.8(38-85) | 61.9±14.4(37.3-87.9) | 1 |
| **Syncytial Knot Index (%)** | 43±16.2(10-70) | 36.9±20.2(0-66.6) | 0.7 |

n = number of subjects, Data is presented in Mean ±SD (range), One way ANOVA test with bonferroni correction; P<0.05, statistically significant

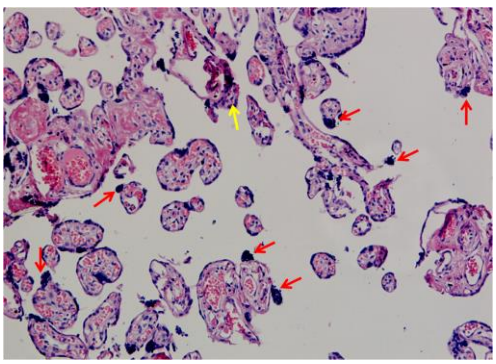

**Figure 1. Photomicrograph of Early Onset Preeclamptic Placenta (Hematoxylin and Eosin staining) showing syncytial knots (red arrows) and deformed villous (yellow arrow)**

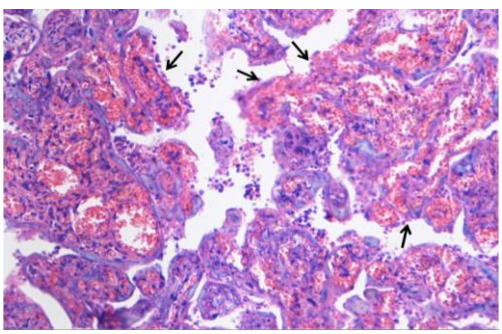

**Figure 2. Photomicrograph of Early Onset Preeclamptic Placenta (Hematoxylin and Eosin staining) showing increased capillarisation and deformed villi (black arrows)**

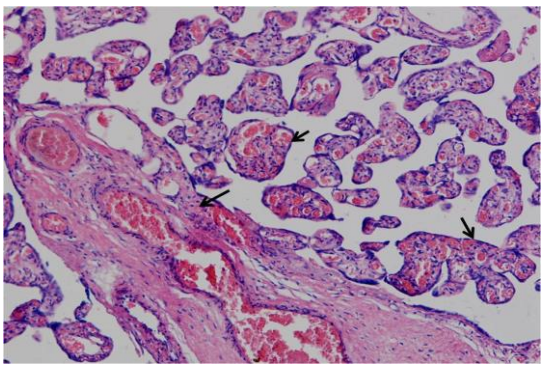

**Figure 3. Photomicrograph of Late Onset Preeclamptic Placenta(Hematoxylin and Eosin staining) showing the normal morphology of villi (black arrows)**

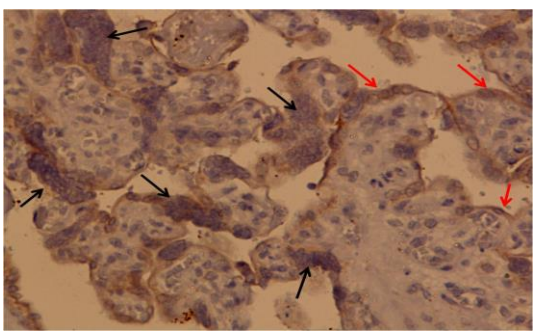

**Figure 4. Photomicrograph of Early Onset Preeclamptic Placenta showing M30 positive trophoblastic cells (red arrows) and syncytial knots (black arrows)**

J Infertil Reprod Biol, 2017, Volume 5, Issue 4, Pages: 20-25. https://doi.org/10.47277/JIRB/5(4)/20

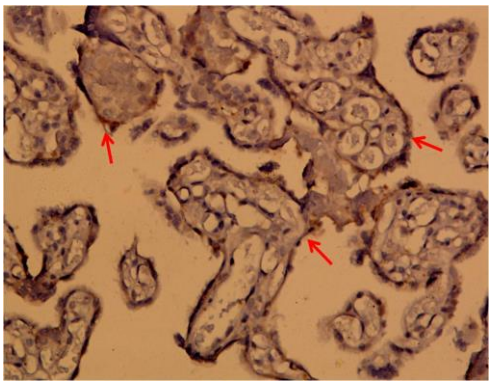

**Figure 5. Photomicrograph of Late Onset Preeclamptic Placenta showing less number of M30 positive trophoblastic cells (red arrows)**

## Discussion

Various hypotheses have been postulated to unravel the complex pathogenesis of preeclampsia but its exact etiology still remains to be elucidated. The proposed sequence of placental events includes the accelerated trophoblastic apoptotic process causing formation of more syncytial knot aggregates (stage 1) that get shed into maternal circulation and stimulate the maternal immune system that ultimately results in endothelial dysfunction (stage 2). The abnormal functioning of these endothelial cells leads to the vascular compromise and clinical manifestations of preeclampsia (9). Many studies have been aimed to find the factors released into circulation that may link to placental abnormalities and maternal disease which usually starts many weeks after placentation is over (10). It has been well documented that syndrome of pregnancy induced hypertension manifests at different gestational ages. Though the preeclamptic women in both the early and late onset groups may present with cardinal features of hypertension and proteinuria but the underlying pathological events may greatly differ. The increased maternal age is one of the risk factors of preeclampsia (11). Our study shows that both the early and late onset preeclamptic groups are associated with increased maternal age. Both the groups also showed raised SBP, DBP and proteinuria as compared to the control group. Among the two subsets, it was the early onset preeclamptic group which showed higher range of these parameters indicating its severity and poor maternal response.

The ongoing pathogenetic changes in preeclampsia are the abnormal placentation and placental vascular insufficiency due to exaggerated rate of trophoblast apoptosis. This leads to intrauterine growth restriction (12). Our results show that in the early onset preeclamptic group, the low birth babies were born prematurely with low APGAR scores. In most of the cases of this group, the newborns were delivered by caesarean sections. All these results indicate poor fetal responses in early onset preeclamptic group. Fetal responses in late onset preeclamptic group were comparable to that of control groups.

The decreased placental weight and altered morphological features in early onset preeclamptic group suggest the underlying aberrant placentation. The other feature of placentopathy observed in this group was increased rate of trophoblastic apoptosis which burdens the placenta thereby depleting the maternofetal interface and release of increased syncytial knots as shown with our results. The clinical implications of aberrant apoptotic pathway have already been discussed in multiple reviews (13). The excessive rate of trophoblast apoptosis produces a greater number of syncytial knots that may undergo necrosis and later stimulate maternal immune system (14,15). Although the cases of infertility are rising in India but pregnancy related complications such as preeclampsia and endometrial related disorders are equally troublesome (16-18). Early onset preeclampsia is itself a maternal risk factor as chances of severe maternal inflammatory syndrome will be more by the time of delivery. The late onset preeclamptic group did not show any significant pathological changes as by this stage, placenta has already developed. The pathological events might be occurring in the maternal endothelium which could be responsible for the clinical manifestations in this group.

## Conclusion

The comparative maternal and fetal clinical parameters along with placental pathological changes provide evidence which suggests that preeclampsia exists as etiologically heterogenous disorder. Among the preeclamptic groups, maternal, fetal and placental responses were severely derranged in early onset preeclamptic group as compared to the late onset preeclamptic group. On the other side, the fetal and placental responses in late onset preeclamptic group were comparable to that of control group. As shown in earlier studies, our study also suggests that the early onset preeclampsia is a placental as well as maternofetal disorder whereas late onset preeclampsia is purely a maternal disorder and therefore, placental dysfunction is not a prerequisite for the development of late onset preeclampsia. The maternal risk factors which can be attributed to the immune response in late onset preeclamptic group are the nutritional, genetic, immunological or environmental. The maternal inflammatory response ultimately leads to vascular compromise the hallmarks of which are the ischemia, inflammation and oxidative stress causing clinical manifestations of this syndrome.

The future advancements in immunology, genetics and epidemiology can provide a promising area of interest to unravel the underlying pathogenetic events of preeclampsia and subsequent maternal inflammatory responses. The early onset preeclampsia remains to be a severe complication that contributes to maternal and neonatal morbidity and mortality. The current understanding of maternal, fetal and placental responses in early and late onset preeclampsia definitely indicate different etiological factors for these subsets of hypertensive disorders.

## References

1. Brown MA, Lindheimer MD, de Swiet M, et al. The classification and diagnosis of hypertensive disorders of pregnancy: statement from the international society for the study of hypertension in pregnancy(ISSHP). Hypertens Pregnancy. 2001;20:9-114.
2. Allaire AD, Ballenger KA, Wells SR, et al. Placental apoptosis in preeclampsia. Obstetrics and Gynecology. 2000;96:271-276.

3. Sharma M, Kumar R, Dhingra R. Apoptosis : Understanding of the signaling pathways. International Journal of Biological and Medical Research. 2012;3(1):2306-2308.
4. Huppertz B, Frank HG, Kingdom JC, et al. Villous cytotrophoblast regulation of the syncytial apoptotic cascade in the human placenta. Histochemistry and Cell Biology. 1998;110:495-508.
5. Sharma M, Kumar R, Dhingra R. An immunohistochemical study of the syncytial knots in the preeclamptic placentas. International Journal of Pharmaceutical Research and Bio-Science. 2012;1(4): 228-239.
6. Peter VD, Magee LA, Roberts JM. Subclassification of preeclampsia, Hypertension in pregnancy. 2003;(22)2:143-148.
7. Sharma M, Kumar R, Bhatla N, Dhingra R. A comparative study of apoptosis in placentas of normal and preeclamptic Indian pregnant women by TUNEL assay and M30 immunostaining. Journal of Clinical Laboratory Analysis. 2012;(26):459-466.
8. Sharma M, Kumar R, Dhingra R. Apoptosis: Searching for the detection techniques. International Journal of Biological and Medical Research. 2012;(3)1: 2305–2308.
9. Lucilla P. Endothelial dysfunction of preeclampsia. Pharmacological Reports. 2006; 58: 69-74.
10. Rinehart BK, Terrone DA, Lagoo-Deenadayalan S, et al. Expression of the placental cytokines tumor necrosis factor , interleukin 1 and interleukin 10 is increased in preeclampsia. American Journal of Obstetrics and Gynecology. 1999;181:915-920.
11. Yamada Z, Kitagawa M. Effect of maternal age on indices of apoptotic and proliferative cells in human placenta. Molecular Human Reproduction. 2001;7:1179-1185.
12. Roberts JM, Gammill HS. Preeclampsia: Recent insights. Hypertension. 2005;46:1243-1249.
13. Sharma M, Kumar R. Apoptosis: Researching the clinical implications. J. Int. Med. Sci. Acad. 2014;(27)3:161-162.
14. Gupta AK, Hasler P, Holzgreve W, et al. Induction of neutrophil extracellular DNA lattices by placental microparticles and IL8 and their presence in preeclampsia. Human Immunology. 2005; 66(11): 1146-1154.
15. Sharma M, Dhingra R, Kumar R. Relevance of placental pathological changes of maternal inflammatory syndrome along with obstetric and clinical parameters in preeclampsia. International Journal of Scientific and Research Publications. 2012;2(8):1-8.
16. Yadav A, Arora M, Saini V, et al. Serum gonadotropin and prolactin levels in females with primary infertility and thyroid dysfunction in North Indian population. Journal of Infertility and reproductive Biology. 2014;(2)3:88-91.
17. Kanza MR. The Expression of β-Catenin in the Epithelial Cells and Stromal Cells of Endometriosis and normal endometrial cells. Journal of Infertility and reproductive Biology. 2014;(2)3:70-76.
18. Javed A, Ashwini LS, Ganguly D, et al. Assisted conception, endometrial tuberculosis with secondary infertility, treatment and subsequent live birth. A case report. Journal of Infertility and reproductive Biology. 2015;(3)3:208-212.