International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(RESEARCH ARTICLE)

Check for updates

Expression of androgen receptor in human placentas from normal and preeclamptic pregnancies

Megha Hasmukh Lalcheta [1,*], S R Niveditha [1] and Vivek Pramod Vithalani [2]

[1] *Department of Pathology, Kempegowda Institute of Medical Sciences, Bangalore, Karnataka, India.*
[2] *Department of Gynecology, Vithalani Hospital, Jamnagar, Gujarat, India.*

International Journal of Science and Research Archive, 2023, 10(01), 873–882

Publication history: Received on 06 September 2023; revised on 13 October 2023; accepted on 16 October 2023

Article DOI: https://doi.org/10.30574/ijsra.2023.10.1.0841

Abstract

Background: Human placenta is a diary of all the prenatal events and it's study may provide valuable insight into pathophysiology of many diseases. One such disease preeclampsia (PE) is a leading contributor of maternal/fetal mortality and morbidity. In a quest to improve the treatment protocols, newer etiologies are researched, the latest being Androgen Receptor (AR) expression in PE placentae.

Methodology: Study was conducted in a tertiary care hospital in Bengaluru over a period of 18 months. Placentae (15) from singleton pregnancies with PE formed the study group while placentae (5) from normotensive pregnancies were the control group. Gross and histopathological findings followed by immunohistochemistry of AR was performed on all placentae and categorized based on the percentage of villi stained. Intracellular localisation and the type of cells staining were also recorded.

Results: Mean age was 28 years, majority (73%) of PE were in 28-32 weeks gestation group, with 46% being primigravidae. Past history of PE was observed in 75% while 53% had family history of PE. Decreased placental weight, increased syncytial knots, accelerated villous maturation and stromal fibrosis, fibrinoid necrosis and mural hypertrophy of arterioles were statistically significant findings in PE group. AR staining was seen in 16/20 (80%) with 11/15 PE cases showing 2+ and 3+ staining. Cytoplasmic staining was commonly seen in Syncytiotrophoblast, Cytotrophoblast & stromal cells in both groups.

Conclusion: AR expression was seen both in PE and non-PE placentae, although AR expression is increased in the former. Stillbirths were associated with positive AR despite clinically classified as mild PE, while negative AR was associated with live births. AR expression could be a new marker for PE with adverse outcome especially in recurrent cases.

Keywords: Preclampsia; Placenta; Androgen receptor; Immunohistochemistry; Vasculopathy

1. Introduction

PreEclampsia (PE) is a human pregnancy syndrome characterized by hypertension and proteinuria after 20 weeks of gestation[1]. Worldwide, PE has been leading contributor of maternal and perinatal morbidity, with up to 4.3% neonatal deaths [2]. Incidence of PE is 5.6% in India [3]. Unfortunately, the cause of PE remains unclear to date. PE is associated with abnormal placentation early in pregnancy, and is considered an important initial event [4]. Various studies to study the pathogenesis of PE are happening worldwide to develop effective treatment protocols. In the past many years, dysregulation of steroid hormones, specifically increases maternal testosterone levels, has become an important

* Corresponding author: Megha Hasmukh Lalcheta

endocrinopathy repeatedly associated with clinical manifestations of PE [5]. In this direction, new markers are studied and one of them being androgen receptor (AR) expression in PE placentas.

Preeclamptic women have elevated androgen levels and AR gene expression. It has been hypothesized that androgens affect vascular function, and vascular smooth muscle is involved in the development of PE. Moreover, it is postulated that an abnormal levels of androgens negatively impacts placental angiogenesis and/or alters trophoblast cell proliferation and differentiation[1, 5] although the exact mechanisms are unclear. Increased AR expression may alter AR-mediated function on sycytiotrophoblasts and stromal cells in placenta, and be a possible mechanism for its association with PE [6].

Treatment options for PE are limited using antihypertensives, such as methyldopa, hydralazine, labetalol and nifedipine[7], and magnesium sulfate for prevention of eclamptic seizures[8]. These treatments have limited efficacy, and the only cure is the delivery of the placenta with baby, which will have a totally undesired outcome especially before 34 weeks gestation. In order to develop more effective therapeutic interventions for PE, it is important to understand the role of AR in maternal vascular and placental function, as well as blood pressure control, during normal pregnancy and in PE.

2. Materials and methods

The current study was an observational study with sample size of 20 specimens which were collected from the department of OBG, KIMSH & RC and transferred to histopathology section, in the department of Pathology, KIMS Central Laboratory, Bengaluru, Karnataka between January 2020 to July 2021. Placentae from singleton pregnancy with PE [PE definition: A previously normotensive pregnant woman whose blood pressure reaches 140/90 mm Hg or greater after 20 weeks gestation on at least two occasions has *pregnancy induced hypertension* and significant proteinuria (1+ or greater on urine dipstick confirmed by a 24h collection containing > 300 mg of protein)] were included in inclusion criteria. Placentae from pregnant women with singleton pregnancies without hypertension or proteinuria were taken under the control group. This study excluded Placentas from twin pregnancies and poorly fixed placental specimens.

The Objectives of the current study were to compare the expression of AR in placenta of normal and pre-eclamptic cases in singleton pregnancies and to explore the expression of AR with gestational age, fetal sex, placental morphology.

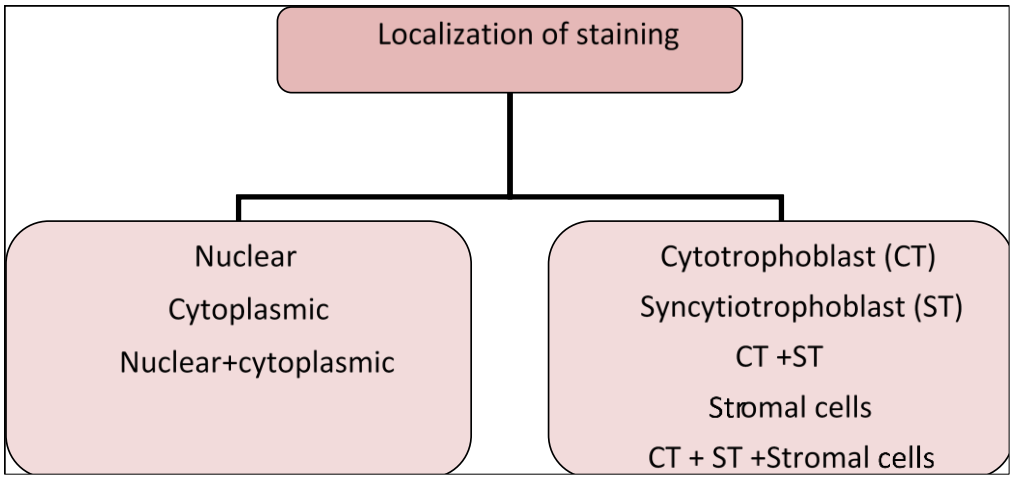

Figure 1 Criteria for localization of AR staining

Placental gross examination was done after fixation in 10% formalin for a minimum of 3 days. Bits were taken for histopathological studies from the appropriate sites e. g. maternal surface, foetal surface of placenta, membranes, in the margin umbilical cord, infarcted, hemorrhagic area if any. Tissues were processed routinely by Leica TP 1020 tissue processing unit. Sections of 3-5 micron thickness was obtained from paraffin embedded blocks and routinely stained with Haematoxylin & Eosin. Under light microscopy, microscopic features were divided into vascular and villous lesions of PE. Important vascular lesions like acute atherosis, fibrinoid necrosis, thrombosis and mural hypertrophy of arterioles. common villous lesions like increased syncytial knots, acceleratred villous maturation, cytotrophoblastic proliferation, stromal edema, stromal fibrosis, hyalinization and calcification were observed.

This study used Rabbit anti-human Androgen Receptor Antibody (Clone SP107), Dako real envisions detection system, DBS Company, prediluted form of Androgen Receptor (AR) immunomarker on selected block after initial histopathological examination. Control blocks was selected in-house from prostate samples. AR expression was considered to be positive when brown granular staining was seen either in trophoblasts (CT&/ST), villous stromal cells or decidual cells, either in nuclear/cytoplasmic or both. AR positivity was expected to be expressed both in normal and PE placentae[6]. Hence, an indigenous scoring system based on % of stained cells was formulated. ≤30% → 1+, 31-80% → 2+, >81% → 3+. Another criterion which was considered was the localization of the staining. (Figure 1)

3. Results

Over a period of 18 months, a total of 20 placentae (15 preeclamptic & 5 normal) were studied. Out of the 15 cases of PE, two were of the severe PE with blood pressure of > 160/110 mmHg. One having platelet count <1 lakh/cumm and the other is having creatinine level >1.1 mg/dl. Age of the patients in the study group ranged from 21 to 36 years with majority (46.7%) in 26-30 years. 73% of PE group & 80% in control group were in 28-32 weeks of gestation. Primigravidae comprised the majority (7/15 i.e. 46.7%) in the study group. There was no statistical significance between study and control group for comparing parity and age group. 75% of multipara women had past history of PE. In the study group, majority (53.3%) had mild protenuria. Grade of proteinuria increased as the mean BP increased. In most cases of PE, placentae were small when compared to the control group. Weight of the placenta in study group ranged from 140-180 gms with a mean of 305.67 gms. The mean weight of placenta in control group was 342 gms.

Eccenteric cord insertion was noted in 10 cases (66.7%) of PE and 1 (20%) in control group. Retroplacental hematoma was seen in 5 (33.3%) PE cases. Infarction was observed as significant finding grossly in 10/15 (66.7%) cases. None of the control group cases showed retroplacental hematoma and infarction. [Figure 2 (A & B)]

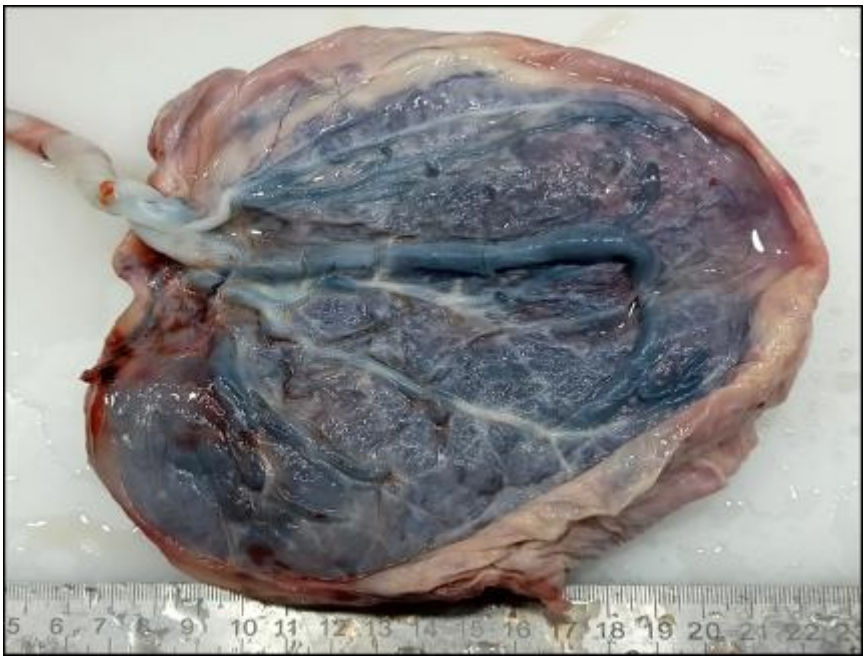

Figure 2 (A) Gross findings in PE cases - Eccentric cord insertion

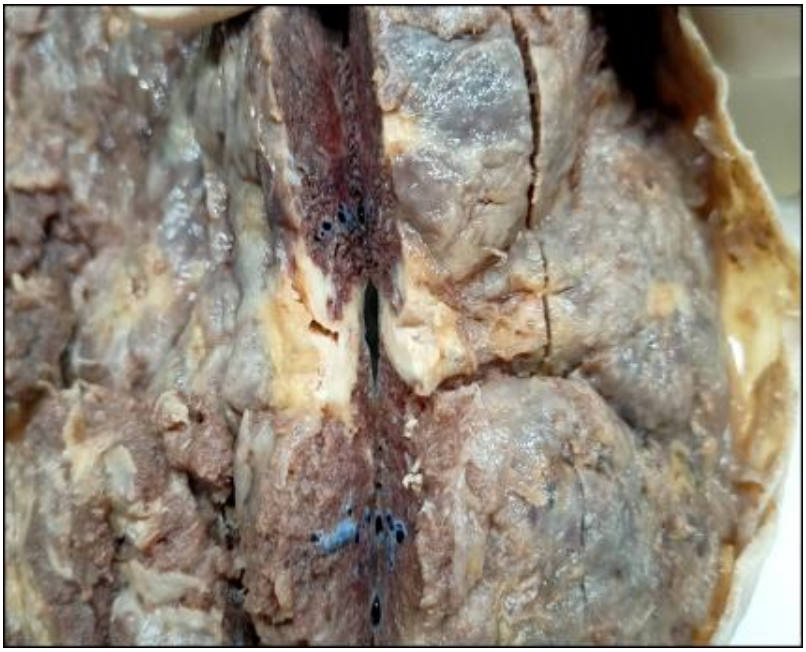

Figure 2 (B) Gross findings in PE cases – Infarction in the center

Histopathology features were observed and categorised as villous and vascular findings. More than 125-130 syncytial knots per 100 villi are considered as significant, 14/15 (93.3%) PE cases showed increased number of syncytial knots. All 15 PE cases showed accelerated villous maturation. Also seen are cytotrophoblastic maturation in 2 (13.3%) cases, stromal oedema in 1 case, stromal fibrosis in 80% cases, hyalinization and calcification in 26.7% and 86.7% cases respectively. (Table 1)

Table 1 Comparison of Villous lesions - Decidual arteriopathy between 2 groups using Chi Square Test (n=20)

Variable	**Category**	**Study**		**Control**		**P-Value**
		n	**%**	**n**	**%**	
Increased Syncytial knots	Yes	14	93.3%	2	40.0%	0.01*
	No	1	6.7%	3	60.0%	
Accelerated villous maturation	Yes	15	100.0%	0	0.0%	<0.001*
	No	0	0.0%	5	100.0%	
Cytotrophoblastic proliferation	Yes	2	13.3%	0	0.0%	0.39
	No	13	86.7%	5	100.0%	
Stromal oedema	Yes	1	6.7%	0	0.0%	0.55
	No	14	93.3%	5	100.0%	
Stromal fibrosis	Yes	12	80.0%	0	0.0%	0.002*
	No	3	20.0%	5	100.0%	
Hyalinization	Yes	4	26.7%	0	0.0%	0.20
	No	11	73.3%	5	100.0%	
Calcification	Yes	13	86.7%	1	20.0%	0.005*
	No	2	13.3%	4	80.0%	

[* The Level of signifcance was set at p<0.05.]

Mural hypertrophy was seen both in control and study group, while acute atherosis, fibrinoid necrosis, thrombosis were not observed in control group. Mural hypertrophy was seen in all 100% of cases of PE while in control group only 60% showed mural hypertrophy. Of them fibrinoid necrosis & mural hypertrophy of arterioles were statistically significant. (Table 2) [Figure 3 (A, B,)]

Table 2 Comparison of Vascular lesions - Decidual arteriopathy between 2 groups using Chi Square Test (n=20)[* The Level of signifcance was set at p<0.05.]

Variable	**Category**	**Study**		**Control**		**P-Value**
		n	**%**	**n**	**%**	
Acute atherosis	Yes	5	33.3%	0	0.0%	0.14
	No	10	66.7%	5	100.0%	
Fibrinoid necrosis	Yes	13	86.7%	0	0.0%	<0.001*
	No	2	13.3%	5	100.0%	
Thrombosis	Yes	3	20.0%	0	0.0%	0.28
	No	12	80.0%	5	100.0%	
Mural hypertrophy of arterioles	Yes	15	100.0%	2	40.0%	<0.001*
	No	0	0.0%	3	60.0%	

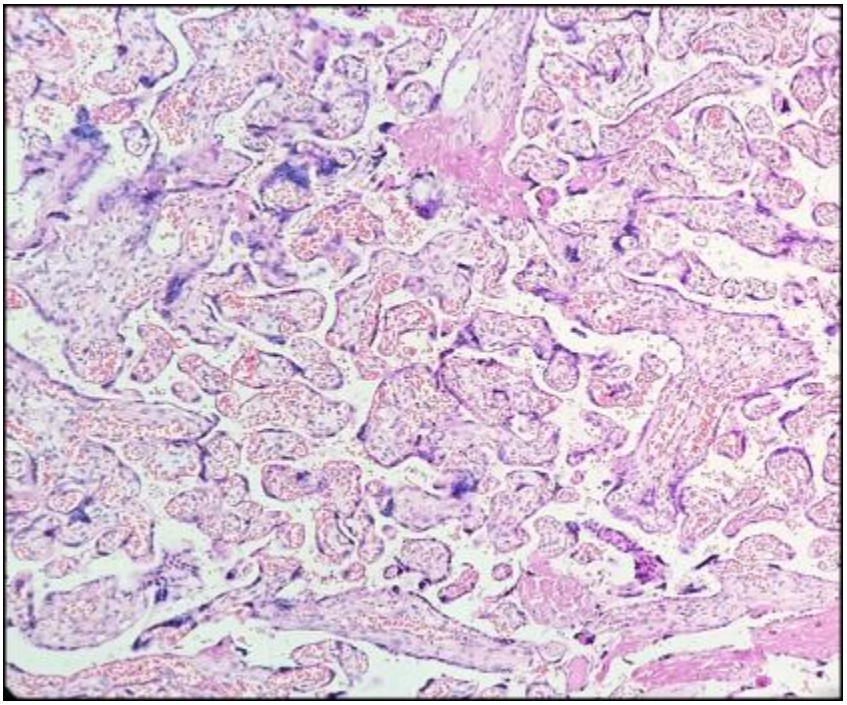

Figure 3 (A) Microscopic findings in PE cases – Increased syncytial knots (H&E, 100x)

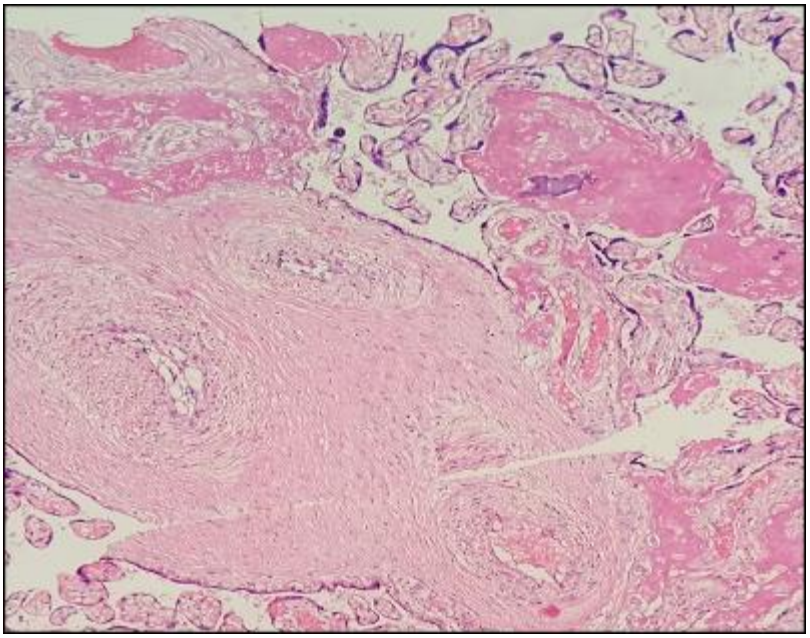

Figure 3 (B) Microscopic findings in PE cases – Fibrinoid necrosis, mural hypertrophy of arterioles, atherosis and calcification (H&E, 200x)

Majority of placentae both from the study and control group i.e. 16/20 showed AR staining, control group showed AR staining of 1+ in majority (80%) while the study group showed 1+ staining in only 33% of cases. Of the 11 cases with AR staining in study group (PE), about 77% showed staining of 2+ and 3+ while in control group 80% showed 1+ staining. In study group, AR expression was mostly seen in CT, ST (CT+ST=36.4%) and in equal number of cases, AR staining was observed in CT, ST and stromal cells (36.4%). However, in one case, decidual cells also joined ST, CT & stromal cells in expressing AR. Intracellular localisation of AR wasalso studied revealing majority in cytoplasmic location both in study (6/11) and control group (3/5). (Table 3)

Table 3 Comparison of Expression, Localization, site & intensity of Androgen Receptor between 2 groups using Chi Square Test (n=20)

Variable	**Category**	**Study**		**Control**		**P-Value**
		n	**%**	**n**	**%**	
Expression	Negative	4	26.7%	0	0.0%	0.28
	1+	5	33.3%	4	80.0%	
	2+	4	26.7%	1	20.0%	
	3+	2	13.3%	0	0.0%	
Localization	Nuclear	4	36.4%	1	20.0%	0.73
	Cytoplasmic	6	54.5%	3	60.0%	
	Nuclear+Cytoplasmic	1	9.1%	1	20.0%	
Site	Stromal cells	2	18.2%	3	60.0%	0.15
	ST	0	0.0%	1	20.0%	
	CT, ST	4	36.4%	0	0.0%	
	CT, ST & Stromal cells	4	36.4%	1	20.0%	
	CT, ST, Stromal cells, decidua	1	9.1%	0	0.0%	

Though the comparison of AR staining in both control and study groups were not statistically significant, AR expression was more (2+ and 3+ staining) in PE cases. Cytoplasmic staining was commonly seen in trophoblastic cells and stromal cells of both PE & control group placentae. [Figure 4 (A, B)]

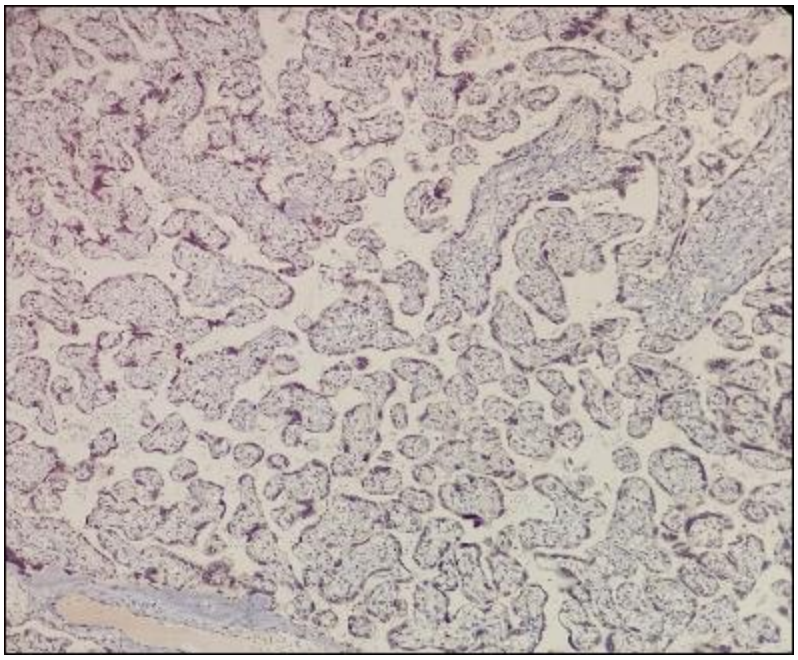

Figure 4 (A) AR staining seen in more than 80% of villi, given as 3+ (IHC, Dako, 200x)

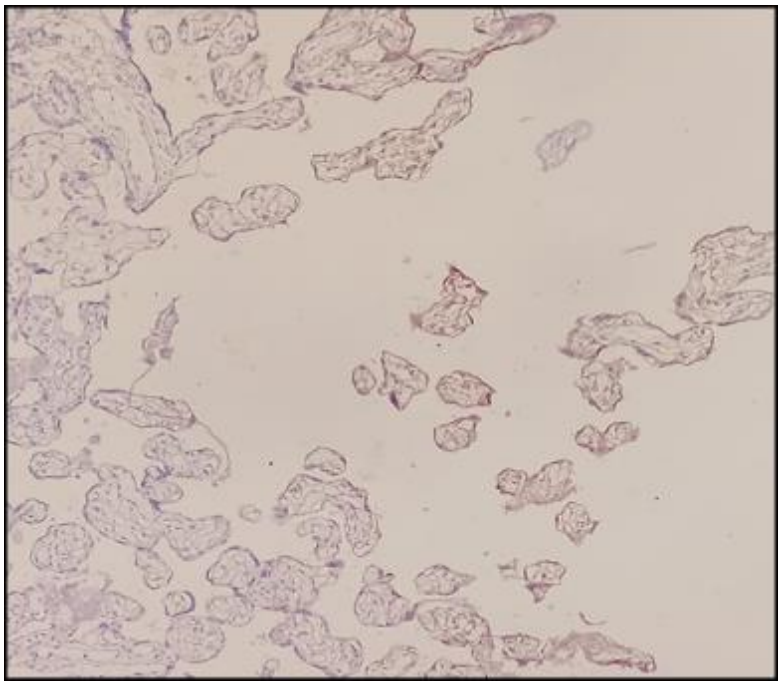

Figure 4 (B) AR staining seen in 31- 80% of villi, given as 2+ (IHC, Dako, 200x)

4. Discussion

PE is a multi-organ disorder of pregnancy and has a significant role of maternal morbidity and mortality worldwide[9]. From all maternal deaths, India accounts for 17 % worldwide[10]. The hypertensive disorders of pregnancy (HDPs) are

responsible for ~14 % of all maternal deaths, with little change in rates in recent years[11]. The most dangerous of the HDPs, PE, is typically defined as the onset of new hypertension with significant proteinuria in pregnancy[12]. Preeclampsia (PE), beyond the immediate threat of fetal loss, also risks the progression to eclampsia & thereby increased maternal morbidity. The role of steroids in ER, PR, glucocorticoids on placental physiology is well established. However the role of androgen in pregnancy adaptation is poorly understood.

Lamminpää R et al[13] found in his study that the mean ages of the control (<35) and study groups (≥35) were 26.6 ± 4.2 years and 37.5 ± 2.3 years, respectively. In the present study however the mean age was lesser. Ezeigwe et al[14] in their study observed that 40% (22/54) of PE cases were primigravidae. The present study with 46.7% (7/15) primigravidae is comparable with the above study. Past history/or family history of PE have been shown to be associated with PE and is one of the risk factors[15,16,17]. In the present study 75% (6/8) multiparous women had past history, while positive family history was seen in 53% of PE cases in our study. In a primigravida, a family history of PE is associated with a fourfold increased risk of severe PE [18].

Decreased weights of placentas were associated with PE, and more strongly with preterm than term PE. Salmani D et al[19] also observed the weights of the placenta in study groups were below 500 gms. The mean placental weight in the present study is 305.67 gm in PE group and 342 gm in control group.

Only 3% cases showed marginal insertion of the umbilical cord in the study done by Salmani D et al [19]. In the present study this was seen in 10 cases of PE group. Gross pathological changes are most common with severe PE occurring preterm[20]. In the current study, 66.7% (10/15) cases showed infarction from the PE group which is statistically significant compared to control group.(Table 13) There was significant difference between presence of infarction in control group and PIH group (p value 0.001). These findings were similar with the findings of Salvatore et al[21], Gore CR et al[22]. The difference in the presence or absence of retroplacental haematoma between mild PE, severe PE, eclampsia, and control groups was significant in the study done by Ezeigwe C et al[14]. In the present study, retroplacental hematoma was seen in 5 (33.3%) PE cases compared to zero case in the control group.

A significant increase in syncytial knot formation (tenny parker change) in placental villi indicates the disturbance in the hormonal factors, which may probably lead to altered blood flow[19]. Kartha S et al[23], in their study considered >125-150 syncytial knots per 100 villi as significant and as a result 32% of PIH cases showed this finding whereas 16% of control group showed the same finding. The present study had shown the same finding in 93% of PE cases. 2/5 cases in control group also showed increased syncytial knots. Similar to Ojha K et al [24] accelerated villous maturation was seen in almost all cases of PE group compared to the control group. Gore CR et al[22] observed in their study, mean number of cytotrophoblastic proliferation was 16.2 ± 4.27 in PIH group and 3.6 ± 2.57 in control group. In our study, 2 PE cases (13.3%) showed cytotrophoblastic proliferation compared to zero case in control group. Jones et al[25] found significant increase in number of cytotrophoblastic cells in preeclamptic placentae. In the present study, 80% cases in study group showed stromal fibrosis. In the study done by Kartha S et al,[23] stromal fibrosis was observed in 38% of cases. Stromal oedema was observed in 35.7% in mild PE cases whereas in the present study, this finding was seen in 6.7% cases. Hyalinization, in our study was observed in 26.7% cases which are comparable with the study done by Kartha S et al[23] who found hyalinization in 28% of PE cases in their study. Narsimha A et al[26] observed the overall incidence of 26.9%, 22.2% in mild PE and slightly higher (33.3%) in severe PE. The incidence of calcification in PE placenta in the present study was 86.7% which is comparable with the study done by Ojha K et al[24] who found calcification in 94.54% cases of study group.

Acute atherosis is considered as a part of decidual vasculopathy & is associated with severe hypertension and poor fetal outcomes. The present study showed acute atherosis in 33.3% PE cases. Kartha S et al[23] found acute atherosis in 16% of PE cases whereas Kim YM et al[27] found acute atherosis in 10.2 % from the study group. According to De Wolf F et al[28] acute atherosis is a lesion limited to blood vessels that have not been altered by the normal adaptive processes of implantation suggestive of vascular maladaptation which has lead to endothelial injury. Fibrinoid necrosis was observed in 86.7% PE cases in the current study whereas it has been observed in 19% PE cases in Kartha S et al[23] study and 32.72% in Ojha K et al[24] study, in their study group. Mural hypertrophy is commonly observed wherever there is maternal vascular underperfusion like in PE but also has been observed in non-PE cases but to a lesser extent.[22] In this study also mural hypertrophy of arterioles is not only observed in all the study cases (100%) but also in 40% of control cases. Ezeigwe C et al[14] in their study showed statistical significant analysis in decidual arteriopathy, accelerated villous maturation, and cytotrophoblastic proliferation between the severe preeclampsia, eclampsia, and the control groups. In the present study, vascular lesions such as fibrinoid necrosis (p-value<0.001) & mural hypertrophy of arterioles (p-value <0.001) were statistically significant. Villous lesions such as increased syncytial knots (p-value <0.01), stromal fibrosis (p-value 0.002), accelerated villous maturation (p-value <0.001) and calcification (p-value <0.005) were also statistically significant.

Placental androgen action is mediated by a complex network of pathways and pregnancy morbidities may arise from perturbed placental androgen signaling which leads to fetal morbidity and mortality.[6] In current study AR was expressed, both in PE and normotensive placentae. However, the percentage of villi showing AR expression was higher (2+ & 3+) in PE placentae Hsu T Et al[6] in their study demonstrated that both normal and PE placentae expressed AR and the findings of current study are concordant with this study. AR expression was positively associated with infarction, decidual vasculopathy features (fibrinoid necrosis, mural hypertrophy of arterioles, acute atherosis) and villous features like accelerated villous maturation and increased syncytial knots. Though the sample size was small, findings of this study does strongly reinforce the role of AR in PE. 4 cases of PE placentae showed complete negative AR staining. All these 4 cases were less than 30 weeks of gestation and probably agrees with the study by Chan et al[29] and hypothesis by Hsu T et al[6] that there is very little / absent AR expression in early human placenta. Hsu T et al[6] suggested that greater the gestational age, greater AR expression in women placentae. Research in novel therapeutic agents to counteract the effects of androgens and over expression of AR in PE placentae seems promising. There is a tendency of clinical medicine to seek out single tests, but till date such an attempt has been futile. The vascular maladaptation in PE is perhaps a complex interplay of factors and hormones which may be confined to only placenta, hence AR alone may not answer all the questions.

5. Conclusion

In the present study negative AR staining was observed in early gestation while as the gestational age progressed the AR expression increased. AR expression is seen in both normal and PE placentas but in increased percentage in the latter as seen in our study. Early detection, careful monitoring, and treatment of PE are crucial in preventing mortality related to this disorder. At the same time, AR negativity seemed to be associated with better fetal outcome. Confirmation of the study findings in Indian scenario may open the gates for revolutionary treatment protocols for PE.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors'.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Palomba S, de Wilde MA, Falbo A, Koster MP, La Sala GB, Fauser BC. Pregnancy complications in women with polycystic ovary syndrome. Human Reproduction update. 2015, 21(5):575-592.

[2] Cherian AG, Paul E, Helan J, Aabidha PM. Maternal and fetal outcome in preeclampsia in a secondary care hospital in South India. Journal of Family Medicine and Primary Care. 2015, 4(2):257–260.

[3] Sajith M. Incidence of pregnancy induced hypertension and prescription pattern of antihypertensive drugs in pregnancy. International Journal of Pharma Sciences and Reaserch. 2014, 5(4):163-170.

[4] Roberts JM, Redman CW. Pre-eclampsia: more than pregnancy-induced hypertension. Lancet 1993, 341, 1447–1451.

[5] Kumar S, Gordon GH, Abbott DH, Mishra JS. Androgens in maternal vascular and placental function: Implications for preeclampsia pathogenesis. Reproduction. 2018, :R155–R167.

[6] Hsu T, Lan K, Tsai C, Ou C, Cheng B, Tsai M et al. Expression of Androgen Receptor in Human Placentas from Normal and Preeclamptic Pregnancies. Taiwanese Journal of Obstetrics and Gynecology. 2009, 48(3):262-267.

[7] Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstetrics and Gynecology. 2013 Nov, 122(5):1122-1131.

[8] Al Khaja KAJ, Sequeira RP, Alkhaja AK, Damanhori AHH. Drug treatment of hypertension in pregnancy. Journal of Hypertension. 2014, 32(3):454–63.

[9] Mou A, Barman Z, Hasan M, Miah R, Hafsa J, Das Trisha A et al. Prevalence of preeclampsia and the associated risk factors among pregnant women in Bangladesh. Scientific Reports. 2021, 11(1). https://doi.org/10.1038/s41598-021-00839-w

[10] Vidler M, Charantimath U, Katageri G, Ramadurg U, Karadiguddi C, Sawchuck D et al. Community perceptions of pre-eclampsia in rural Karnataka State, India: a qualitative study. Reproductive Health. 2016, 13(S1). https://doi.org/10.1186/s12978016-0137-9

[11] Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. The Lancet. 2005, 365(9461):785-799.

[12] World Health Organization. WHO Recommendations for Prevention and Treatment of pre-Eclampsia and Eclampsia. 2011. http://apps.who.int/iris/bitstream/10665/44703/1/9789241548335_eng.pdf.

[13] Lamminpää R, Vehviläinen-Julkunen K, Gissler M, Heinonen S. Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland 1997–2008. BMC Pregnancy and Childbirth. 2012, 12(1). https://doi.org/10.1186/1471-2393-12-47.

[14] Ezeigwe C, Okafor C, Eleje G, Udigwe G, Anyiam D. Placental Peripartum Pathologies in Women with Preeclampsia and Eclampsia. Obstetrics and Gynecology International. 2018, 2018:1-8.

[15] Khalil G. Preeclampsia: Pathophysiology and the Maternal-Fetal Risk. Journal of Hypertension and Management. 2017, 3(1). doi.org/10.23937/2474-3690/1510024

[16] Bej P, Chhabra P, Sharma AK, Guleria K. Determination of risk factors for preeclampsia and eclampsia in a tertiary hospital of india: A case control study. Journal of Family Medicine and Primary Care. 2013, 2(4):371-375. doi: 10.4103/2249-4863.123924

[17] Paré E, Parry S, McElrath TF, Pucci D, Newton A, Lim KH. Clinical risk factors for preeclampsia in the 21st century. Obstetrics and Gynecology. 2014, 124(4):763-770.

[18] Cincotta RB, Brennecke SP. Family history of pre-eclampsia as a predictor for preeclampsia in primigravidas. International Journal of Gynaecology and Obstetrics. 1998 Jan, 60(1):23-7.

[19] Salmani D, Purushothaman S, Somashekara SC, et al. Study of structural changes in placenta in pregnancy-induced hypertension. Journal of natural science, biology and medicine.2014, 5(2):352-355.

[20] Roberts D, Post M. The placenta in pre-eclampsia and intrauterine growth restriction. Journal of Clinical Pathology. 2008, 61(12):1254-1260.

[21] Salvatore CA. The placenta in acute toxemia. A comparative study. American Journal of Obstetrics and Gynecology.1968, 102(3):347-353.

[22] Gore CR, Pandey A, Shetty A, Rao A, Paranjape S. A study on histopathological changes in placenta in pre-eclampsia/eclampsia: A case-control study in tertiary care centre, western India. Indian Journal of Pathology and Oncology.2018, 5(3):385-390.

[23] Kartha S, Poothiode U, Jayalakshmy PS. Placental Pathology in Pregnancy Induced Hypertension. Journal of Evolution of Medical and Dental Sciences 2014, 3:9272-8.

[24] Ojha K, Rawal S, Jha A. Placental Pathology in Severe Pre-eclampsia and Eclampsia. Nepalese Medical Journal. 2018, 1(1):32-35.

[25] Jones CJP, Fox H. An ultrastructural and ultrahistochemical study of the human placenta in maternal pre-eclampsia. Placenta. 1980, 1(1):61–76.

[26] Narsimha A, Vasudeva D. Spectrum of changes in placenta in toxemia of pregnancy. Indian Journal of Pathology and Microbiology. 2011, 54(1):15-20. doi: 10.4103/0377-4929.77317

[27] Kim YM, Chaemsaithong P, Romero R, Shaman M, Kim CJ, Kim JS et al. The frequency of Acute Atherosis in Normal Pregnancy and Preterm Labor, Preeclampsia, Small for Gestational Age, Fetal Death and Midtrimester Spontaneous Abortion. J Matern Fetal Neonatal Med. 2015, 28:2001-09.

[28] De Wolf F, Robertson WB & Brosens I. The ultrastructure of acute atherosis in hypertensive pregnancy. American Journal of Obstetrics and Gynaecology 1975, 123:164-174.

[29] Chan CC, Lao TT, Ho PC, Sung EO, Cheung AN. The effect of mifepristone on the expression of steroid hormone receptors in human decidua and placenta: A randomized placebo-controlled double-blind study. The Journal of Clinical Endocrinology & Metabolism. 2003, 88(12):5846–50.