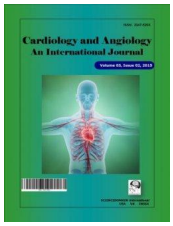

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Can We Predict Preeclampsia?

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Authors' contributions

This work was carried out in collaboration between both authors. Author JR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author NS managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Hypertensive disorders in pregnancy are a leading cause of peripartum morbidity and mortality. Preeclampsia is a heterogeneous maternal syndrome.

Large studies have pointed out the association of impaired spiral artery remodeling at the fetomaternal interphase in preeclampsia, but how exactly is the fetomaternal dialogue mediated and what are the biomarkers to detect the subclinical disease in various subsets of high-risk pregnancies is still a challenge. These biomarkers can finally be used to diagnose renal function (Kallikrein-creatinine ratio), vascular resistance (uterine artery Doppler), coagulation disorders (platelet volume, fibronectin, prostacyclin, thromboxane, oxidant stress (lipid peroxidase, 8-isoprostane, antioxidants, anticardiolipin antibodies, homocysteine, serum uric acid), vascular adaptation (Placental growth factor, Vascular endothelial growth factor, s flut, s eng) and markers of placental function and ischemia (placental CRH, CRH bp, activin, inhibin,hCG).Post partum preeclampsia can be predicted by identifying the factors preventing the excretion of sodium, puerperal diuresis and shift of intravascular fluid into the extra vascular compartment compartment(atrial natriuretic peptide in the first week after delivery, natriuresis and inhibition of aldosterone, angiotensin II, vasopressin)

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Keywords: Preeclampsia; trophoblast; prediction; hypertension; pregnancy.

ABBREVIATIONS

JZ	:	*Junctional zone*
VEGF	:	*Vascular endothelial growth factor*
PLGF	:	*Placental growth factor*
HLAG	:	*Human leukocute antigen-G*
SLE	:	*Systemic lupus erythematosus*
APLA	:	*Antiphospholipid antibody syndrome*
CRH	:	*Corticotropin hormone*
CRH bp	:	*Corticotropin hormone binding protein*
HCG	:	*Human chorionic gonadotropin*
sFLUT	:	*soluble FMS like tyrosine kinase*
sENG	:	*soluble endoglin*
COMT	:	*Catechol-O-Methyl transferase*
IDO	:	*Indolamine 2,3 deoxygenase*
PGE2	:	*Prostaglandin E2*
uNK	:	*Uterine natural killer cells*
MMP	:	*Matrix metalloproteinases*
TGFβ	:	*Transformation growth factor β*
TIMP	:	*Tissue inhibitor of metalloproteinases*
KIR	:	*Killer immunoglobulin like receptor*
CD94	:	*Cluster of differentiation 64*
NKG2	:	*Natural killer group 2*
TCR	:	*T cell receptor*
PT	:	*Proliferative extravilloustrophoblast*
IT	:	*Invasive extravillous trophoblast*
Th2	:	*T cell (helper) 2*

1. INTRODUCTION

In human placental bed, at the feto maternal interface, the extravillous trophoblastic cells invade not only the decidua but also the subendometrial or Junctional Zone (JZ) myometrium [1,2,3]. The interstitial and endovascular migratory cells in the in the vessels wall were later confirmed to be trophoblastic in origin [4,5].

Brosen et al suggested that at “physiological change” of spiral arteries in the pregnant uteri was a result of the destructive action of invading trophoblast on vascular smooth muscles and elastic membranes [6]. Later a maternal contribution had to be considered since some changes in the maternal vessel wall precede the antidromic migration of trophoblast along the vessel lumen. Some researchers believe that the local intravasation of interstitial trophoblast is more likely [7].

The four steps in which remodeling takes place is well documented [8]. The first is the decidua associated remodeling. Perivascular sheaths of swollen decidual cells (streeter’s column) appear as early as postovulatory day 11 [3]. These swollen perivascular cells may be derived from vascular smooth muscles. As early as 9 weeks the uterine decidual natural killer cells secrete Vascular Endothelial Growth Factor (VEGF), Placental growth Factor (PLGF) and angiopoietins [9,10]. This leads to vacuolation and disorganization of vascular intima and endothelial cells. In JZ myometrium since the natural killer cells are absent the presence of interstitially invading trophoblast may help the release of VEGF and angiopoietins [9,10]. This is evidenced by the fact that the interstitial trophoblast invades the JZ at 8 weeks (Fig. 1 A and 1B).

This is followed by the actual trophoblastic interstitial and intra-arterial migration (Fig. 1 C and 1D). Invasion follows an interstitial and an endovascular course. The endovascular course happens in spiral arteries but never in veins. Interstitial trophoblast, but not endovascular, subsequently fuses to form multinuclear giant cells [11]. Though the multinuclear giant cells appear more striking but it is the mononuclear cytotrophoblast that is most invasive and it occupies extensive area of uterine wall within a short time. An overwhelming number of basophilic mononuclear cells occupy the space between the smooth muscles of JZ myometrium. Quantitative study reveals that there distribution is at the center at 8 to 14 weeks towards a biphasic distribution at 16-18 weeks, thus following a ring like pattern towards the periphery of placental bed [12]. It is thought that after their fusion to form giant cells they lose some potential of invasion. During endometrial decidualization a selective breakdown of extracellular matrix components occurs independent of trophoblastic action.

The interstitial invasion of decidua and JZ myometrium precedes the spiral artery invasion by several weeks. In early pregnancy mononuclear trophoblasts plug the outlets of spiral arterioles at the fetomaternal interface and thus create a low oxygen environment for the developing placenta and fetus. After 10 weeks the whole length of the spiral arteries in decidua may contain trophoblast reaching even up to the superficial vascular JZ Myometrium. Deep

invasion of myometrial segments of the spiral arteries is not seen before 15 weeks.

The third step is trophoblast associated remodeling when the trophoblast cells are actually incorporated into the arterial wall (Fig. 1 E). This vascular incorporation is initiated by the penetration of the endothelium. Electron micrograph revealed that the trophoblast penetrates between the healthy endothelial cells and cross the underlying basement membrane. The smooth muscle penetration ultimately leads to its replacement by trophoblast embedded within a fibroid matrix, probably secreted by the trophoblast itself. The intraluminal trophoblasts now assume a spider like shape because of increasing accumulation of fibrinoid materials around the cell processes. As a rule the intraluminal trophoblast remains mononuclear or at the most become binuclear. This is a contrast to the interstitial trophoblast.

The fourth step re-endothelialization definitely occurs. It is not clear whether the maternal vascular lining is repaired by endothelial remnants which were still present after the intramural invasion or whether a new endothelial covering is derived from circulating endothelial progenitor cells (Fig. 1F).

Investigations of Jauniaux have outlined the different times in gestation at which the decidual spiral arteries and junctional zone spiral arteries get remodeled in decidual association (step 1) and endovascular trophoblast association (step 2). Placental oxygenation increases as gestation advances (Fig. 2). There is no connection between the spiral arteries and the intervillous space at 7 weeks. And they appear at 8 weeks. Even before this communication the decidual spiral arteries have remodeled (Fig. 2). At 7 to 10 weeks there is first wave of remodeling of decidual spiral arteries and early rise of intervillous flow. The second wave of remodeling, from 15 weeks onwards, in which the endovascular trophoblast is observed in the junctional myometrium, is well after the steep rise in placental oxygenation. The decidua associated

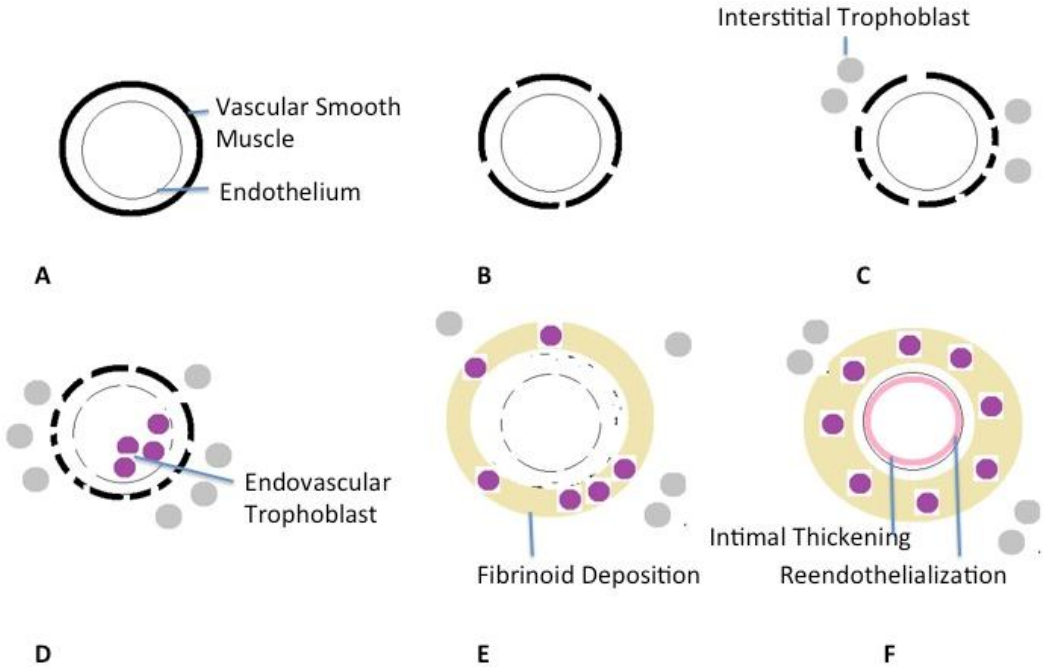

Fig. 1. Diagrammatic representation of spiral artery remodeling steps. A. Unmodified spiral artery showing endothelium and vascular smooth muscle. B. Step 1,Decidua associated remodeling with disorganization of vascular smooth muscles. C. Step 2, Interstitial Trophoblast migration enhances vascular smooth muscle disorganization D. Endovascular Trophoblast temporarily replaces to endothelium E. Step 3, Intramural incorporation of endovascular trophoblast and deposition of fibrinoid, replacing the vascular smooth muscle F. Step 4, Reendothelialisation and intimal thickening

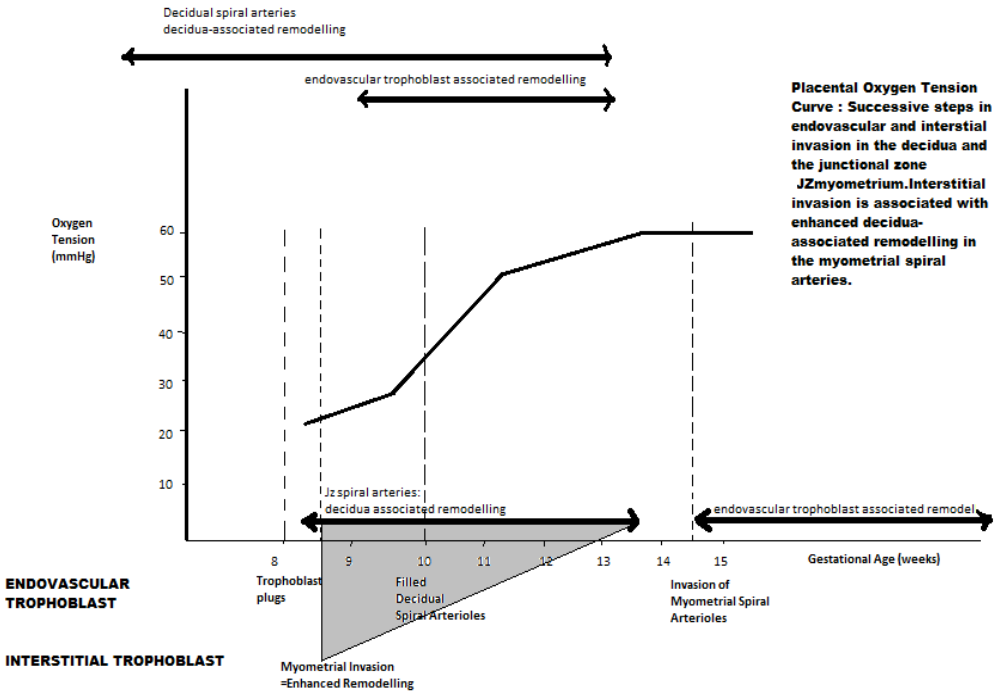

Fig. 2. Placental Oxygen Tension Curve: Successive steps in endovascular and interstitial invasion of decidua and the Junctional Zone endometrium. Interstitial invasion is associated with enhanced decidua associated remodeling in myometrial spiral arteries (Shaded Triangle)

spiral remodeling of myometrium happen at 8 -14 weeks, while trophoblastic associated remodeling of myometrium happens only after 15 weeks. The early decidua associated remodeling of junctional myometrium essentially prepares for the rise in uteroplacental flow, while the subsequent trophoblast associated remodeling only stabilizes the vessel and the increased flow is maintained.

2. TOPOLOGY OF VASCULAR REMODELING

A lateral gradient of diminished invasion has been seen at the periphery of placental bed as compared to the center of placental bed. Even in normal pregnancies the junctional myometrium spiral arteries are remodeled only at the center and there is absence of junctional zone myometrial vascular remodeling at the periphery of placental bed. In preeclampsia the trophoblast associated remodeling is restricted to the decidual spiral arteries even in the center of placental bed. One study demonstrated that even decidual segments might show incomplete remodeling. It is imperative that the placental bed should be biopsy be taken from an adequately central space and not lateral. There are less interstitial giant cells in the myometrium and more stacked endometrial glands pushed by the placenta at the periphery of the placental bed.

2.1 Failure of Remodeling

Failure of Step 1: Decidua associated remodeling is defective

Late luteal phase secretory endometrium and Decidualisation is associated with infiltration of natural killer cells, which are now considered to be major effector cells at trophoblast –uterine interphase interactions. It has also been postulated that repeated cycles of menstrual shedding of decidualising endometrium may act as preconditioning for successful implantation and deep placentation [13]. This might explain the increased risk of preeclampsia in teenage pregnancy, short interval of pregnancy since menarche and primipaternity. This may also explain the lowered risk of preeclampsia in women who have intercourse earlier with partner who fathers the current pregnancy. Recent research also suggests that natural killer cells associated defects of implantation are due to disturbed ligand receptor interphase. Uterine

natural killer cells are absent in JZ myometrium, but their angiogenic action is mediated by interstitial trophoblast.

Failure of step 2: Failed trophoblastic migration

An impaired rise in blood flow, as a result of improper decidualisation and improper angiogenises leads to a failed integrin shift and a failure of trophoblast to acquire an endothelial phenotype. Disturbed HLA –G expression by trophoblast has also been postulated. This might explain preeclampsia seen in association with molar pregnancy (Fig. 3).

Failure of step 3: Trophoblast associated remodeling is defective

Impaired intramural incorporation of endovascular trophoblast and lack of fibrin deposition can be caused by impaired secretion of proteinases. This may be because of improper trophoblast signaling. This might explain the increased risk preeclampsia in connective tissue disorders, SLE, APLA. The defective laying down of fibrin may explain the preeclampsia in cases of thrombophilia disorders like Factor 2, Factor 5 Leiden factor mutations, serpine gene mutations and Protein C and Protein S deficiencies. This might also explain the association of Preeclampsia with placenta accrete and increta where the nitabuch's layer is absent. Chronic hypertension, renal disease, increased maternal age and diabetes may lead to hyperplasia of smooth muscles of spiral arterial media, this may lead to impaired maintenance of elastin and vascular smooth muscles [14,15]. When these conditions are present sub clinically before pregnancy, the preexisting media hyperplasia might interfere with trophoblast-induced apoptosis of elastic smooth muscles.

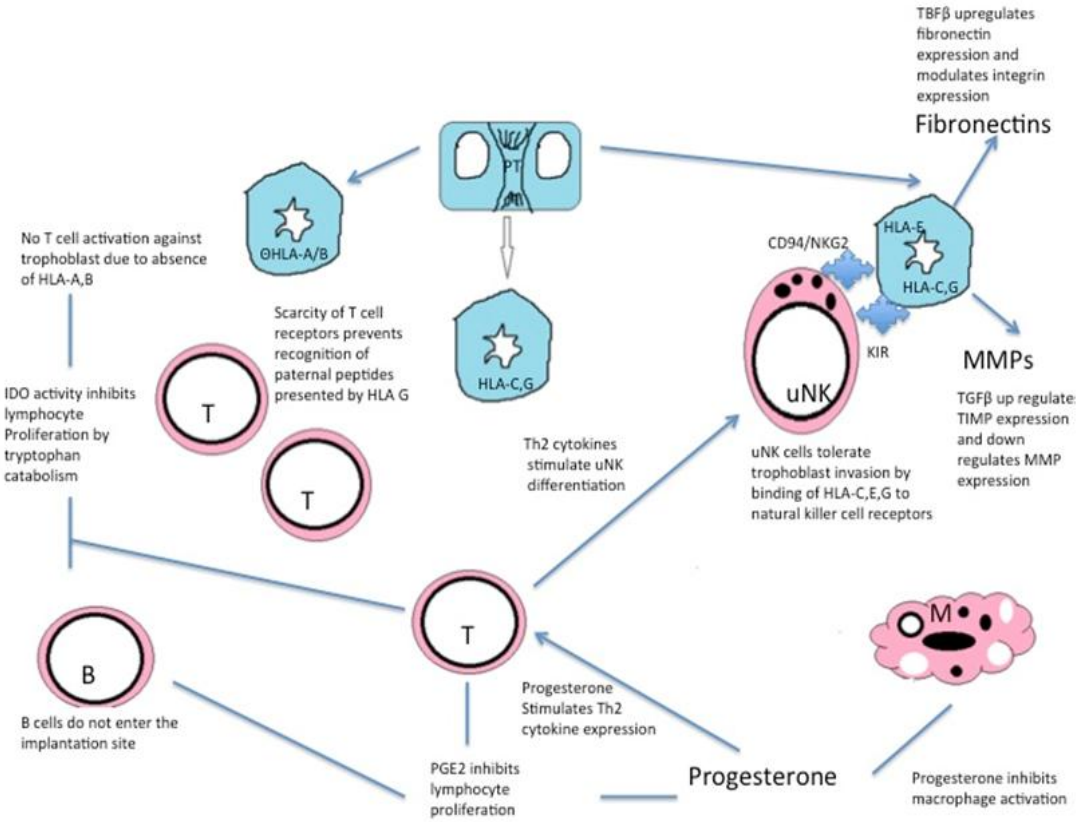

Fig. 3. Schematic diagram of maternal immune cells interacting with trophoblast. Blue are the trophoblastic cells and pink are maternal cells. PT: Proliferative extravillous Trophoblast, IT: Endoluminal Interstitial trophoblast, uNK: uterine natural killer cells, T: T cell, B: B cell

Table 1. High risk characteristics of preeclampsia

High risk	Possible explanation	Prediction by	Clinical features
Teenage pregnancy, short interval of pregnancy since menarche, No prior intercourse and primipaternity.	Defective Infiltration of decidua by natural killer cells, ligand receptor interaction of leukocyte populations	Maternal History	Maternal Syndrome-proteinuria, Hypertension, Edema
Molar pregnancy	Failed trophoblastic migration and intersignal. Ineffective blocking of spiral vessels and oxidative stress and embryo-endometrial interphase	Early first trimester scan	
Reduced vascularity of decidua	Catechol-O-Methyl transferase(COMT) enzyme deficiency that promotes convertion of estradiol to the vasodilator product 2-methyl oxyestradiol	Reduced serum enzyme levels of COMT in third trimester.	
Chronic hypertension, increased maternal age and diabetes	Impaired apoptosis of hyperplastic arterial smooth muscles of spiral arteries	Maternal history, Insulin resistance, Glucose intolerance	
Connective tissue disorders, SLE, APLA.T Factor 2,Factor 5 Leiden factor mutations, serpine gene mutations and Protein C and Protein S deficiencies	Impaired fibrin deposition by trophoblasts	APLA, ANA, Protein essay and genetic screening	
Rh Incompatibility, hyperhomocysteinemia	Exaggerated maternal healing tissue tissue response	ABO incompatibility, Rh Incompatibility screening	
Vascular Resistance	Noncompliant maternal cardiovascular system, Gants Roll over test	Uteroplacental artery flow waveforms, Angiotensin II type 1 receptor agonistic antibodies	
Oxidant stress(Hypoxia or ischaemia-reperfusion injury,increased concentration of xanthine dehydrogenase to xanthine oxidase promotes the production of uric acid and superoxide from degraded purines(Xanthine and hypoxanthine)	Lipid peroxidase, 8-isoprostane,, Hypertriglyceridemia, Haemoglobin, Iron, Transferrin, albumin Isoforms,,Xanthine oxidase	Serum levels, Plasma and tissue expression of the long pentraxin 3,Serum uric acid	

High risk	Possible explanation	Prediction by	Clinical features
	,superoxide mutase glutathione peroxidase expression,		
Renal disease	Kallikrein-creatinine	Serum/urine Levels	
Coagulation, fibrinolysis system, Platelet activation, Markers of vascular Function	Platelet volume, Fibronectin, prostacyclin Thromboxane	Serum levels	
Placental ischemia secondary to any of the above	Placental Peptides, CRH, CRH bp, activin, Inhibin, HCG	Ratio of angiogenic (Placental growth factors, VEGF) and Antiangiogenic Factors (s-flut and s-eng)	
Post partum preeclampsia-Inadequate mobilization of liquid from the interstitial and intravascular to extravascular space (6-8 liters of the total body water, return of 950 mEq of total body sodium accumulated during pregnancy).	Factors affecting Increased urinary sodium excretion between three and five days after birth (increase of atrial natriuretic peptide in the first week after delivery, natriuresis and inhibition of aldosterone, angiotensin II, vasopressin)	Central venous pressure and pulmonary capillary wedge pressures, colloid osmotic pressure, pulmonary crept, clinical Congestive heart failure, cerebral edema	Post partum convulsions due to Posterior reversible encephalopathy syndrome –vasogenic edema in posterior brain due to lack of sympathetic modulation.

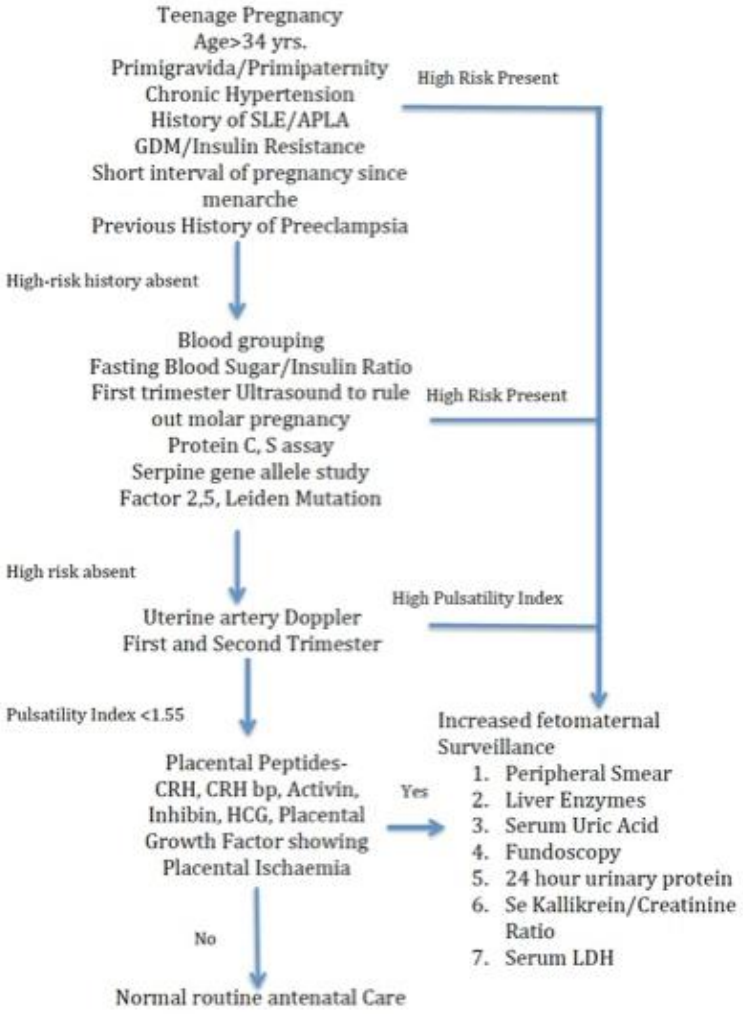

Fig. 4. A clinical algorithm based on clinical, biochemical and ultrasound markers is outlined

Failure of step 4: Increased maternal inflammatory response

Trophoblast proliferation and apoptosis of maternal intra arterial smooth muscles invariable incites maternal tissue repair mechanisms, it is easy to understand that if maternal inflammation is marked the proliferating trophoblast may be destroyed by lipophages resulting in “acute atherosis lesions” in the placental bed [16]. This might explain the occurrence of preeclampsia in Rh incompatible pregnancies and hyper homocysteinemia.

3. CONCLUSION

Preeclampsia is a heterogeneous disease. The late onset preeclampsia at or near term has low fetal and maternal morbidity. But the early onset preeclampsia (1%) of all preeclampsia has significant risks. Prediction of risks and identification of subclinical disease is mandatory. The majority of at risk groups in multigravida are chronic hypertension, pregestational and gestational diabetes, age and multiple fetuses. Whereas, in primi only 14% have theses risks. This suggests that there are multiple underlying etiologies of different clinical presentations. Table 1 summarizes the likely etiopathogeniesis in different clinical scenarios. A clinical algorithm based on clinical, biochemical and ultrasound markers is outlined (Fig. 4). Post partum eclampsia can be predicted and monitored with central venous pressure and pulmonary capillary wedge pressure [17,18,19]. The maternal syndrome (proteinuria, edema and hypertension) also has differences in time of onset, severity and organ system involvement as highlighted in

several studies [20,21,22]. These clinical subpopulations need to be identified and preeclampsia predicted with rigorous definition of different biomarkers of different clinical phenotypes [23,24,25,26,27]. The future endeavors should be to identify subclinical disease in various clinical phenotypes with these potential biomarkers in prospective longidunal studies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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