TRIPLE VESSEL WAVE PATTERN
BY DOPPLER STUDIES IN PRE ECLAMPSIA
AND ITS PERINATAL OUTCOME

Dissertation submitted to

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DECLARATION

I, Dr. SHOBANA PRIYA K solemnly declare that the dissertation titled **"TRIPLE VESSEL WAVE PATTERN BY DOPPLER STUDIES IN PRE ECLAMPSIA AND ITS PERINATAL OUTCOME"** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award , degree, diploma to any other University board either in India or abroad.

This is submitted to The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of M.S. degree Branch – II (Obstetrics and Gynaecology) to be held in April 2016.

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled titled **"TRIPLE VESSEL WAVE PATTERN BY DOPPLER STUDIES IN PRE ECLAMPSIA AND ITS PERINATAL OUTCOME"** is a bonafide work done by **DR. SHOBANA PRIYA K** under My direct supervision and guidance, submitted to the Tamilnadu Dr. M.G.R. Medical University in partial fulfillment of University regulation for M.S. Branch – II Obstetrics and Gynaecology degree examination of The Tamilnadu Dr.M.G.R Medical University to be held in April 2016

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LIST OF ABBREVATION

mmHg	–	millimeter of mercury
BMI	–	Body mass index
GHT	–	Gestational hypertension
MTHFR	–	methylene tetra hydro folate reductase
AGT	–	Angiotensinogen gene
TNF	–	Tumor necrosis factor
IL	–	Interleukin
PG	–	Prostaglandin
DIC	–	Dissemenated intravascular coagulopathy
IUGR	–	Intrauterine growth retaradation
IUD	–	Intrauterine death
HCG	–	Human chorionic gonadotrophic hormone
AFP	–	Alpha fetoprotien
PAAP-A	–	Pregnancy associated plasma protein
VEGF	–	Vascular endothelial growth factor
SD	–	Standard deviation
S/D Ratio	–	Systolic / diastolic ratio
EDF	–	End diastolic flow
PI	–	Pulsatality index
RI	–	Resistance index
AEDF	–	Absent end diastolic flow
REDF	–	Reverse end diastolic flow
UA	–	Umbilical artery
NNC	–	Neonatal complication
EDN	–	End diastolic notch
IDF	–	Increased diastolic flow

ABSTRACT

INTRODUCTION:

The increasing incidence of pre eclampsia necessitates its early detection and intervention for a better perinatal outcome. Doppler plays a significant role in antepartum fetal surveillance. Early and accurate detection of abnormal doppler velocimetry demands the Obstetrician to plan accordingly and thereby improving the perinatal outcome.

AIMS AND OBJECTIVES:

To study the association between pre eclampsia and abnormal doppler velocimetry of triple vessel Uterine artery, Umbilical artery and Middle cerebral artery.

Perinatal outcome with abnormal doppler velocimetry in patients with pre eclampsia

MATERIALS AND METHODS:

All antenatal patients who deliver in the department of Obstetrics and Gynaecology, Chengalpattu Medical College and Hospital during the period of febraury 2015 to September 2015. 200 Patients were taken for my study. Out of which 100 belong to control group and 100 were in study group. Doppler pattern was studied in Uterine artery, Umbilical artery and Middle cerebral artery for all pre-eclampsia patients.

RESULTS:

Umbilical artery and middle cerebral artery doppler abnormality are a better indicator of perinatal outcome.

In the study with uterine artery, 27% were found to have abnormal pattern ,27% with uterine artery high resistance and 28% showed uterine artery early diastolic notch in study group.

With the study of umbilical artery in the study group, 55% were found to have abnormal pattern, 56% with umbilical artery high resistance , 54% with absent end diastolic flow and 29% with reversed end diastolic flow.

17% were found to have abnormal middle cerebral artery pattern among the study group.

Cesarean section rate incidence was higher in the study group (43%) compared with the control group (17%).

Neonatal mortality accounted to 8% which is similar to Mikovic study et all.

Those who have abnormal doppler velocimetry, there is an increased incidence of still birth and IUD when compared to control group.

CONCLUSION:

APGAR rate for babies with abnormal Doppler velocimetry are low when compared to control group. And also the incidence of neonatal complications after birth is also increased with abnormal dopper velocimetry. The incidence of caesarean section rate is increased among abnormal Doppler velocimetry.

Thus Doppler velocimetry is a major support for the conventional antepartum surveillance especially in pre eclampsia.

Abnormal doppler velocimetry alarms the obstetrician to plan the pregnancy in a tertiary care centre with a better NICU setup as it warrants effective monitoring of the patient and expert neonatal care

INTRODUCTION

Pre eclampsia is defined as the presence of systolic blood pressure more than 140 mmhg and diastolic blood pressure more than 90 mmhg , along with proteinuria in pregnant women . It usually occurs after 20 weeks of pregnancy or sometimes earlier when there is multi-fetal pregnancy or molar pregnancy.

The incidence is 5- 10 % of pregnancies. It is a pregnancy specific disease and is associated with high maternal and fetal morbidity and mortality.

Berg and colleagues reported that 16% of 3201 maternal death in the united states from 1991 to 1997 were complications of gestational hypertension . During this study, black women had 3% times higher mortality compared with the white women.

The pathophysiology is characterized by a failure of trophoblastic invasion of spiral arterioles, leading to the maladaptation of maternal spiral arterioles which is associated with increased vascular resistance of the uterine artery and decreased perfusion of the placenta.

Spiral arterioles plays an significant role in pre eclampsia. The structural and physiological changes in the normal spiral arterioles may lead to the development of pre eclampsia.

The precise cause of the vascular endothelial dysfunction , an important factor in etiopathogenesis of pre-eclampsia remains unclear.

The complications of severe pre eclampsia could be prevented by prompt diagnosis of high risk cases, antenatal care and timely intervention.

Doppler plays a significant role in antepartum fetal surveillance. Early and accurate detection of abnormal doppler velocimetry demands the Obstetrician to plan accordingly and thereby improving the perinatal outcome.

AIMS AND OBJECTIVES

To study the association between pre eclampsia and abnormal doppler velocimetry of triple vessel -Uterine artery, Umbilical artery and Middle cerebral artery.

Perinatal outcome with abnormal doppler velocimetry in patients with pre eclampsia.

REVIEW OF LITERATURE

HISTORY

History of eclampsia starts from Hippocratic writings(430-330 BC). In the year (384 – 322 BC) Aristotle was the first to realise that the fetal nutrients are transferred through the umblical cord , which is the only source of connection between the mother and fetus. He also realised that the fetus is fully surrounded by membranes. De-La Motte , in the year 1726, considered that unless associated with convulsions , the oedema is mostly benign.

In 18th century, the idea of proteinuria linked with eclampsia was identified and during the same period, association between oedema, headache and blurred vision were also remarked.

In 19th century, pre eclampsia was studied in a large manner. As a result of these researches, hypertension was identified as an important factor in pre eclampsia. The triad of oedema, hypertension and proteinuria which often precedes the convulsion was came to known as pre eclampsia.

In 1924, renowned scientist Husselman identified that primigravida is eight times more prone to have eclampsia than multigravida. He also found that there is a six fold increased risk of eclampsia in twin pregnancy.

In 1926- 1936, Herrick and co workers found that the essential hypertension is a highly associated factor in hypertensive disorders of pregnancy.

Dickmann in 1952, found that when hypertensive disorders are present in a pregnant woman, she might have either nephritis or essential hypertension.

Redman in 1991, attributed preeclampsia to be an inadequate response of the mother to fetus.

Gill in 1994, postulated the familial nature in pre eclampsia.

Christian Andreas Doppler and the Doppler theory:

The Doppler effect is " apparent change observed in the frequency of a sound wave caused by relative motion between the source and the observer". The Doppler effect applies only when the motion is directly towards or away between the source and the observer. This was discovered by an Australian physicst & Mathematician, "Christian Andreas Doppler".

The Seattle research team developed pulsed wave Doppler equipment for the first time. This research team was headed by Dennis Watkins, John Rein and Donald Baker. The project was started way back in 1966. Duplex instrumentation was also first constructed by this Seattle team. Single transducer crystal does both Doppler and imaging function on a time-sharing basis. This is helpful for the operator to detect the target of Doppler insonation by the Duplex Doppler technique. This discovery marks a milestone in the obstetric and gynaecological field.

Development of colour Doppler USG:

"Single line of ultrasound beam transmission is interrogated in spectral Doppler USG.. Hemodynamic information provided by the spectral Doppler ultrasound which was based on the single dimension flow velocity had its own limitations. This led to the discovery of two dimensional colour Doppler".

The processing of Doppler ultrasound and signal was based on the studies done by 'Angelson and Kristofferson team' and 'Namekawa et al and team'. The former team used the sophisticated filtration technique applied in the radar system of the target indicator motion. This technique removes the high amplitude/ low velocity signals produced by the vessel wall and tissue movement. The latter team discovered the auto co relation technique which used an auto co relator. This auto co relator has the ability to process the mean Doppler phase shift data from 2D scan.

Entry of Doppler Ultrasound in Obstetrics and Gynaecology:

"Fetal heart movements detection was the pioneered application by the Doppler ultrasound in obstetrics. Further a non invasive continuous electronic fetal heart rate monitoring was discovered. This system utilise a continuous wave Doppler ultrasound to determine the fetal heart rate from the fetal cardiac structures.

Drumm, Fitzgerald and Mc Callum et al reported the application of Doppler velocimetry for the first time in obstetrics. This team was the first to publish a renowned article. This publication lead to an era of intensive research

using the Doppler velocimetry in assessing the different components in maternal and fetal circulation.

Use of two dimensional colour Doppler flow mapping techniques in obstetrics was reported by Devore and associates and Maulik and associates. In both studies the Doppler flow mapping was used to characterize the fetal cardiac flow dynamics. Taylor et al characterised the Doppler waves from ovarian/uterine arterial circulations using the pulse duplex-Doppler instrumentation".

METHODOLOGY

In this study, antenatal pregnant women – Primigravida with Pre- eclampsia were identified and who filled the criteria mentioned above were enrolled as study group. And same number of normotensive patients were enrolled as control group. For each patient, history as mentioned in the proforma was taken followed by a general, physical, systemic and obstetric examination.

Ultrasound was done in these patients and doppler ultrasound of the uterine artery,umbilical artery and Middle cerebral artery were noted.

Doppler ultrasound was done with duplex doppler system.

The patient was placed in supine position with left lateral tilt of 15 degree to avoid caval compression.

UTERINE ARTERY:

Uterine artery was examined with the probe kept 3 cm medial to anterior superior iliac spine and directed towards the lateral wall of the uterus. The cross over of the uterine artery and the external iliac artery was identified and the sample site was chosen. Waveforms were recorded from both uterine arteries.

UMBILICAL ARTERY:

Flow velocity waveforms were recorded from the free floating loops in mid position. The diagnosis of absent end diastolic flow or reversed end diastolic flow were made when same doppler patterns was demonstrated in three separate sampling sites.

MIDDLE CEREBRAL ARTERY:

Waveforms are recorded from MCA as it courses through the lateral sulcus. Colour doppler is used to map at the circle of willis

RESULTS

TABLE 1

DISTRIBUTION OF CASES BASED ON AGE

Age	Control	Study
<20 yrs	6	5
20 - 30 yrs	91	93
> 30 yrs	3	2

In control group, 91% belong to age group 20-30 years, 3% were above 30 years and 3% were less than 20 years

In study group, 93% belong to age group 20-30 years, 2% were above 30 years and 5% were less than 20 years

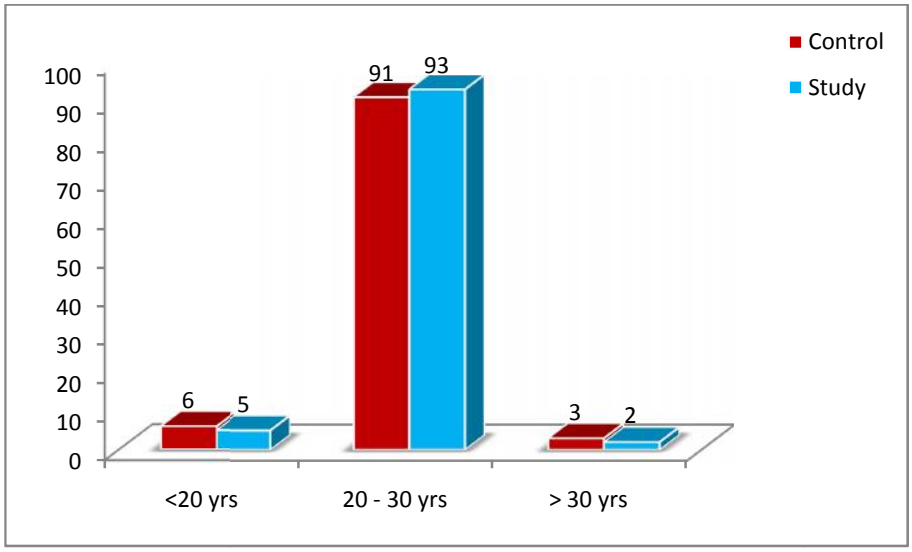


FIG 1: AGE DISTRIBUTION

TABLE 2

UTERINE ARTERY PATTERN DISTRIBUTION

UA pattern	Control	Study
Normal	100	73
abnormal		27

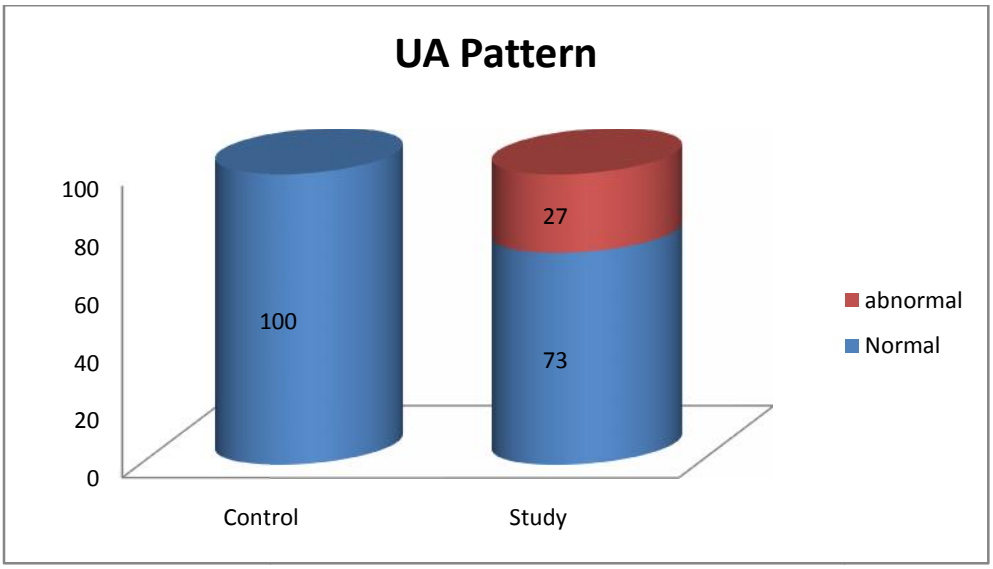


FIG 2: UTERINE ARTERY PATTERN DISTRIBUTION

TABLE 3

UTERINE ARTERY PATTERN AND PERINATAL OUTCOME

Group	APGAR5	>7/10	5/10-6/10	<4/10	Total	Chi sq	p
Control	Normal	96	2	2	100		
Study	Normal	69 (93.2%)	3 (15%)	1 (16.7%)	73	59.19	**0.0001**
	abnormal	5 (6.8%)	17 (85%)	5 (83.3%)	27		
	Total	74	20	6	100		

Group	NNC	Death	Without comp	With comp	Total	Chi sq	p
Control	Normal	1	98	1	100		
Study	Normal	1 (11.1%)	69 (94.5%)	3 (16.7%)	73	63.62	**0.0001**
	abnormal	8 (88.9%)	4 (5.5%)	15 (83.3%)	27		
	Total	9	73	18	100		

TABLE 4

UTERINE ARTERY HIGH RESISTANCE

UA HR	Control	Study
Absent	100	73
Present		27

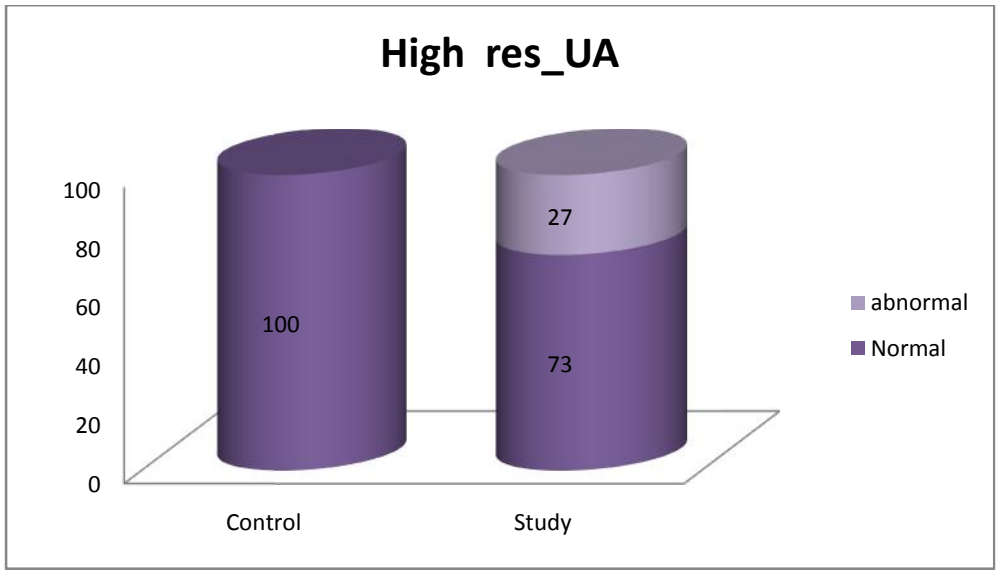


FIG 3: UTERINE ARTERY HIGH RESISTANCE

TABLE 5

UTERINE ARTERY HIGH RESISTANCE AND PERINATAL OUTCOME

Group	Condition	IUD	Still birth	Live born	Total	Chi sq	p
Control	Absent	1	1	98	100		
Study	Absent	0	1 (50%)	72 (76.6%)	73	11.968	**0.003**
	Present	4	1 (50%)	22 (23.4%)	27		
	Total	4	2	94	100		

Group	APGAR1	>7/10	5/10-6/10	<4/10	Total	Chi sq	p
Control	Absent	93	4	3	100		
Study	Absent	48	21 (56.8%)	4 (26.7%)	73	39.04	**0.0001**
	Present	0	16(43.2%)	11 (73.3%)	27		
	Total	48	37	15	100		

Group	NNC	Death	Without comp	With comp	Total	Chi sq	p
Control	Absent	1	98	1	100		
Study	Absent	1 (11.1%)	68 (93.2%)	3 (16.7%)	72	60.08	**0.0001**
	Present	8 (88.9%)	5 (6.8%)	15 (83.3%)	28		
	Total	9	73	18	100		

TABLE 6

UTERINE ARTERY EARLY DIASTOLIC NOTCH

EDN	Control	Study
Absent	100	72
Present		28

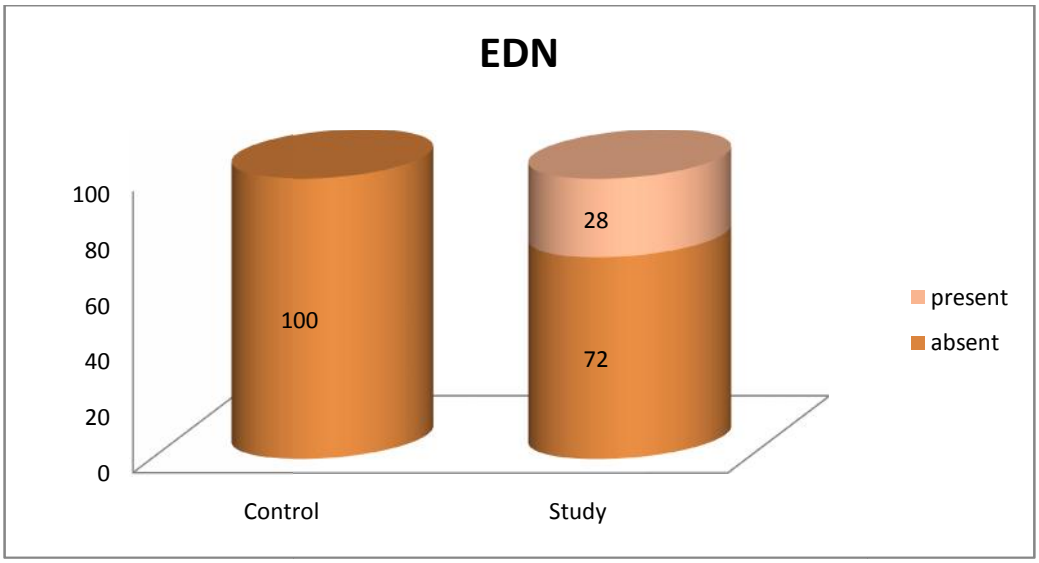


FIG 4: UTERINE ARTERY EARLY DIASTOLIC NOTCH

TABLE 7

EARLY DIASTOLIC NOTCH AND PERINATAL OUTCOME

Group	Condition	IUD	Still birth	Live born	Total	Chi sq	p
Control	Absent	1	1	98	100		
Study	Absent	0	1 (50%)	71 (75.5%)	72	11.35	**0.003**
	Present	4	1 (50%)	23 (24.5%)	28		
	Total	4	2	94	100		

Group	APGAR1	>7/10	5/10-6/10	<4/10	Total	Chi sq	p
Control	Absent	93	4	3	100		
Study	Absent	48	20 (54.1%)	4 (26.7%)	72	39.86	**0.0001**
	Present	0	17 (45.9%)	11 (73.3%)	28		
	Total	48	37	15	100		

Group	NNC	Death	Without comp	With comp	Total	Chi sq	p
control	absent	1	98	1	100		
study	absent	1 (11.1%)	68 (93.2%)	3 (16.7%)	72	60.08	**0.0001**
	present	8 (88.9%)	5 (6.8%)	15 (83.3%)	28		
	Total	9	73	18	100		

TABLE 8

UMBILICAL ARTERY PATTERN

UM pattern	Control	Study
Normal	100	45
Abnormal		55

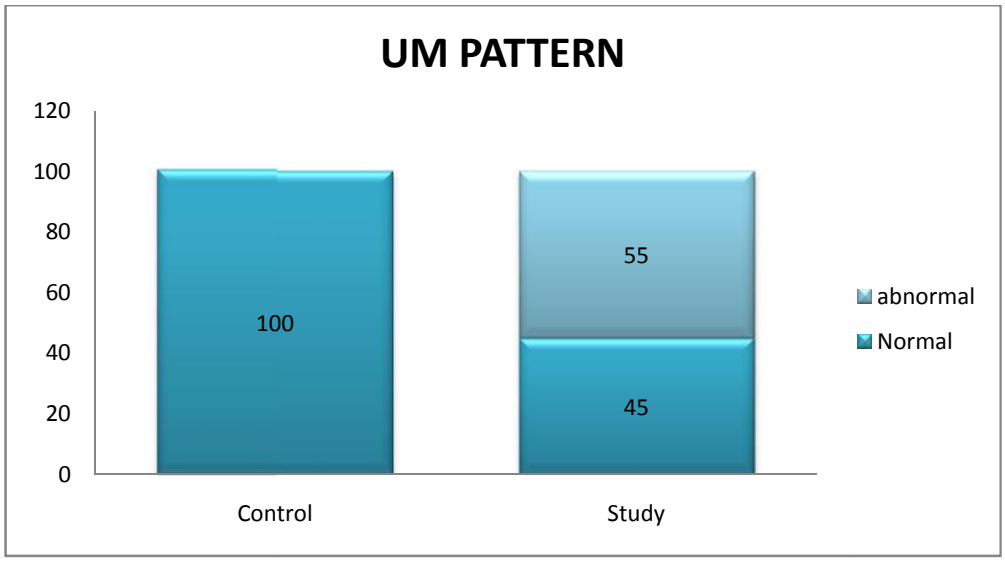


FIG 5: UMBILICAL ARTERY PATTERN DISTRIBUTION

TABLE 9

UMBILICAL ARTERY PATTERN AND PERINATAL OUTCOME

Group	APGAR1	>7/10	5/10-6/10	<4/10	Total	Chi sq	p
Control	Normal	93	4	3	100		
Study	Normal	43 (89.6%)	2 (5.4%)	0	45	74.26	**0.0001**
	Abnormal	5 (10.4%)	35 (94.6%)	15	55		
	Total	48	37	15	100		

Group	NNC	Death	Without comp	With comp	Total	Chi sq	p
Control	Normal	1	98	1	100		
Study	Normal	0	45 (61.6%)	0	45	30.26	**0.0001**
	Abnormal	9	28 (38.4%)	18	55		
	Total	9	73	18	100		

TABLE 10

UMBILICAL ARTERY HIGH RESISTANCE

UM_HR	Control	Study
Absent	100	44
Present		56

TABLE 11

UMBILICAL ARTERY HIGH RESISTANCE AND PERINATAL OUTCOME

Group	APGAR1	>7/10	5/10-6/10	<4/10	Total	Chi sq	p
Control	Absent	93	4	3	100		
Study	Absent	43 (89.6%)	1 (2.7%)	0	44	77.87	**0.0001**
	Present	5 (10.4%)	36 (97.3%)	15	56		
	Total	48	37	15	100		

Group	NNC	Death	Without comp	With comp	Total	Chi sq	p
Control	Absent	1	98	1	100		
Study	Absent	0	44 (60.3%)	0	44	29.06	**0.0001**
	Present	9	29 (39.7%)	18	56		
	Total	9	73	18	100		

TABLE 12

UMBILICAL ARTERY AEDF

UM_AEDF	Control		Study	
	Frequency	Percent	Frequency	Percent
Absent	100	100	46	46
Present			54	54
Total			100	100

TABLE 13

UMBILICAL ARTERY AEDF AND ITS PERINATAL OUTCOME

Group	APGAR1	>7/10	5/10-6/10	<4/10	Total	Chi sq	p
Control	Absent	93	4	3	100		
Study	Absent	44 (91.7%)	2 (5.4%)	0	46	77.62	**0.0001**
	Present	4 (8.3%)	35 (94.6%)	15	54		
	Total	48	37	15	100		

Group	NNC	Death	Without comp	With comp	Total	Chi sq	p
Control	Absent	1	98	1	100		
Study	Absent	0	46 (63%)	0	46	31.5	**0.0001**
	Present	9	27 937%)	18	54		
	Total	9	73	18	100		

TABLE 14

UMBILICAL ARTERY REDF

UM_REDF	Control		Study	
	Frequency	**Percent**	**Frequency**	**Percent**
Absent	100	100	71	71
Present			29	29
Total			100	100

TABLE 15

UMBILICAL ARTERY REDF AND DELIVERY OUTCOME

Group	Condition	IUD	Still birth	Live born	Total	Chi sq	p
Control	Absent	1	1	98	100		
Study	Absent	0	0	71 (75.5%)	71	15.63	**0.0001**
	Present	4	2	23 (24.5%)	29		
	Total	4	2	94	100		

TABLE 16

UMBILICAL ARTERY REDF AND PERINATAL OUTCOME

Group	APGAR1	>7/10	5/10-6/10	<4/10	Total	Chi sq	p
Control	Absent	93	4	3	100		
Study	Absent	47 (97.9%)	24 (64.9%)	0	71	54.29	**0.0001**
	Present	1 (2.1%)	13 (35.1%)	15	29		
	Total	48	37	15	100		

Group	NNC	Death	Without comp	With comp	Total	Chi sq	p
Control	Absent	1	98	1	100		
Study	Absent	0	71 (97.3%)	0	71	9.5	**0.01**
	Present	9	2 (2.7%)	18	29		
	Total	9	73	18	100		

TABLE 17

MCA PATTERN

MCA pattern	Control	Study
Normal	100	83
abnormal		17

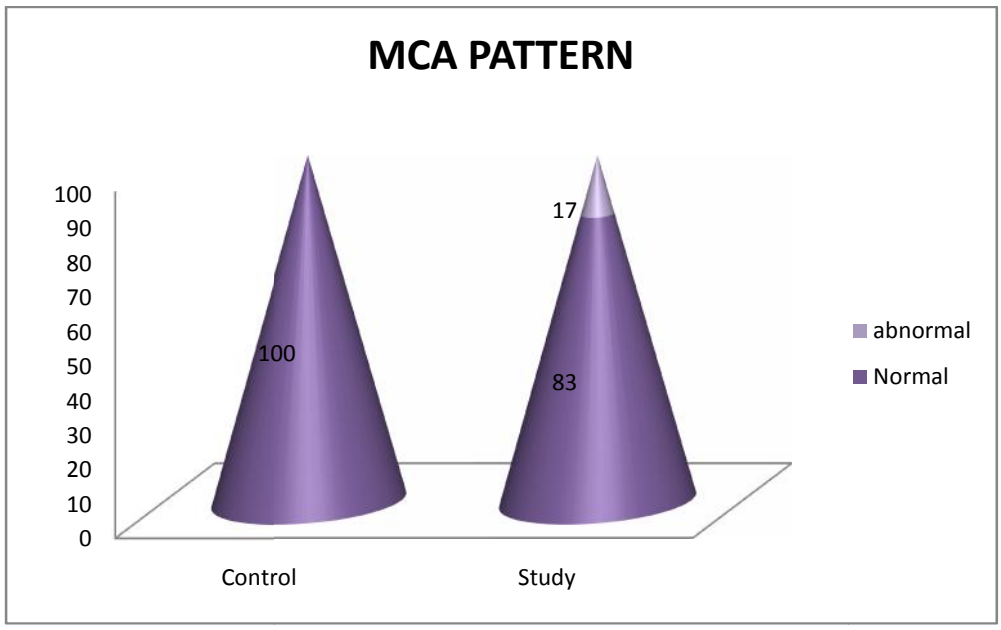


FIG 6: MCA PATTERN DISTRIBUTION

TABLE 18

MCA PATTERN AND DELIVERY OUTCOME

Group	Condition	IUD	Still birth	Live born	Total	Chi sq	p
Control	Normal	1	1	98	100		
Study	Normal	0	0	83 (88.3%)	83	31.16	**0.0001**
	Abnormal	4	2	11 (11.7%)	17		
	Total	4	2	94	100		

TABLE 19

MCA PATTERN AND PERINATAL OUTCOME

Group	APGAR1	>7/10	5/10-6/10	<4/10	Total	Chi sq	p
Control	Normal	93	4	3	100		
Study	Normal	47 (97.9%)	33 (89.2%)	3 (20%)	83	50.76	**0.0001**
	Abnormal	1 (2.1%)	4 (10.8%)	12 (80%)	17		
	Total	48	37	15	100		

Group	NNC	Death	Without comp	With comp	Total	Chi sq	p
Control	Normal	1	98	1	100		
Study	Normal	0	72(98.6%)	11 (61.1%)	83	62.69	**0.0001**
	Abnormal	9	1 (1.4%)	7 (38.9%)	17		
	Total	9	73	18	100		

TABLE 20

MCA IDF

IDF	Control	Study
Absent	100	83
Present		17

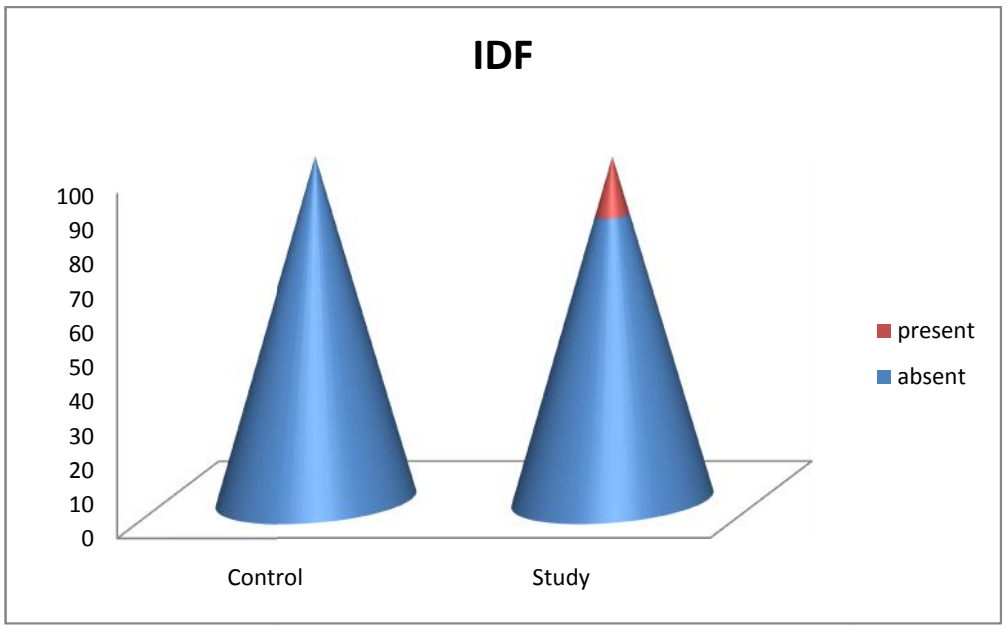


FIG 7: MCA IDF DISTRIBUTION

TABLE 21

MCA IDF AND DELIVERY OUTCOME

Group	Condition	IUD	Still birth	Live born	Total	Chi sq	p
Control	Absent	1	1	98	100		
Study	Absent	0	0	83 (88.3%)	83	31.16	**0.0001**
	Present	4	2	11 (11.7%)	17		
	Total	4	2	94	100		

TABLE 22

MCA IDF AND PERINATAL OUTCOME

Group	APGAR1	>7/10	5/10-6/10	<4/10	Total	Chi sq	p
Control	Absent	93	4	3	100		
Study	Absent	47 (97.9%)	33 (89.2%)	3 (20%)	83	50.77	**0.0001**
	Present	1 (2.1%)	4 (10.8%)	12 (80%)	17		
	Total	48	37	15	100		

Group	NNC	Death	Without comp	With comp	Total	Chi sq	p
Control	Absent	1	98	1	100		
Study	Absent	0	72 (98.6%)	11 (61.1%)	83	62.69	**0.0001**
	Present	9	1 (1.4%)	7 (38.9%)	17		
	Total	9	73	18	100		

TABLE 23

UTERINE ARTERY HIGH RESISTANCE AND DELIVERY

Group	Delivery	Vaginal	Instrumental	LSCS	Total	Chi sq	p
Control	Absent	78	5	17	100		
Study	Absent	52 (92.9%)	1	20 (46.5%)	73	26.88	**0.0001**
	Present	4 (7.1%)	0	23 (53.5%)	27		
	Total	56	1	43	100		

TABLE 24

UMBILICAL ARTERY PATTERN AND DELIVERY

Group	Delivery	Vaginal	Instrumental	LSCS	Total	Chi sq	p
Control	Normal	78	5	17	100		
Study	Normal	43 (76.8%)	1	1 (2.3%)	45	55.72	**0.0001**
	Abnormal	13 (23.2%)	0	42 (97.7%)	55		
	Total	56	1	43	100		

TABLE 25

UMBILICAL ARTERY HIGH RESISITANCE AND DELIVERY

Group	Delivery	Vaginal	Instrumental	LSCS	Total	Chi sq	p
Control	Absent	78	5	17	100		
Study	Absent	42 (75%)	1	1 (2.3%)	44	53.4	**0.0001**
	Present	14 (25%)	0	42 (97.7%)	56		
	Total	56	1	43	100		

TABLE 26

UMBILICAL ARTERY AEDF AND DELIVERY

Group	Delivery	Vaginal	Instrumental	LSCS	Total	Chi sq	p
Control	Absent	78	5	17	100		
Study	Absent	44 (78.6%)	1	1 (2.3%)	46	58.11	**0.0001**
	Present	12 (21.4%)	0	42 (97.7%)	54		
	Total	56	1	43	100		

TABLE 27

UMBILICAL ARTERY REDF AND DELIVERY

Group	Delivery	Vaginal	Instrumental	LSCS	Total	Chi sq	p
Control	Absent	78	5	17	100		
Study	Absent	52 (92.9%)	1	18 (41.9%)	71	31.13	**0.0001**
	Present	4 (7.1%)	0	25 (58.1%)	29		
	Total	56	1	43	100		

TABLE 28

MCA PATTERN AND DELIVERY

Group	Delivery	Vaginal	Instrumental	LSCS	Total	Chi sq	p
Control	Normal	78	5	17	100		
Study	Normal	51 (91.1%)	1	31	83	6.41	**0.04**
	Abnormal	5 (8.9%)	0	12	17		
	Total	56	1	43	100		

DISCUSSION

When the pre eclampsia sets in very early during pregnancy , close monitoring of the patient is necessary. The utero placental circulation is also safeguarded by controlling the high blood pressure.

The identification of the women at risk of pre eclampsia is essential in the antenatal period. The prompt treatment at the initial stage may prevent severe morbidities for both mother and fetus.

HISTORICAL ASPECTS

Historically, this disorder was reported nearly 2000 years back when Celus reported as seizures in pregnant women that occur after delivery.

This abnormality was given the name “ECLAMPSIA” in greek which means lightening , because of its rapid and unexpected appearance.

In the middle of 1800s, urinary examination of proteins in pregnant women with eclampsia revealed that severe proteinuria may antedate seizure.

In the later part of 1800s, when it become possible to measure blood pressure with sphygmomanometer, it is apparent that, high blood pressure antedate the seizures.

HYPERTENSIVE DISORDERS IN PREGNANCY

Hypertensive disorder complicating pregnancy are common and form one of the deadly triad, along with haemorrhage and infection, that continues to be responsible for increased maternal morbidity and mortality related to pregnancy.

CLASSIFICATION

According to working group of National Institute of Health working group on High Blood Pressure in pregnancy(2000) , hypertensive disorders complicating pregnancy are classified into 4 types

Gestational hypertension

Preeclampsia - eclampsia

Pre-eclampsia superimposed on chronic hypertension

Chronic hypertension

The major changes proposed in this classification based on the current evidence were eliminating edema and the change in blood pressure (30 mm rise in systolic and 15 mm in diastolic) as diagnostic criteria , and the adoption of korotkoff phase V to determine diastolic pressure. The term pregnancy induced hypertension was abandoned.

GESTATIONAL HYPERTENSION

It is defined as sustained systolic blood pressure of ≥140 mm hg or diastolic blood pressure ≥ 90 mm hg first time in pregnancy after 20 weeks of gestation. This

is best confirmed when evidence is present on two occasions at least 6 hours apart but within 7days.

Not accompanied by proteinuria. Blood pressure returns back to normal within 12 weeks of postpartum period.

PRE- ECLAMPSIA

It is defined as rise in blood pressure with proteinuria, edema may be present.

Proteinuria ≥300 mg/24 hrs urine collection or 30 mg /dl. That is equivalent to 1+ in dipstick tests in random urine samples

It is classified in to two types,

Non severe pre eclampsia

Severe pre eclampsia

Pre eclampsia is considered as severe if any of the following is present

Systolic blood pressure ≥ 160 mm hg or diastolic blood pressure ≥ 110 mm hg.

Proteinuria more than 5g/ 24 hrs urine collection samples. Or 3+ more on random samples.

Oliguria (less than 500ml/24hours)

Thrombocytopenia (platelets <1 lakh /µL)

Symptoms like persistent headache, visual disturbances, upper abdominal pain.

Convulsion

Microangiopathic hemolysis- increased lactate dehydrogenase

Elevated serum creatinine

Elevated serum transaminase

Pulmonary edema

Fetal growth restriction.

ECLAMPSIA

In a women with pre eclampsia, a convulsion that cannot be attributed to another cause is termed as Eclampsia. The seizures are generalised and may appear before, during, or after labour.

PRE ECLAMPSIA SUPERIMPOSED ON CHRONIC HYPERTENSION

New onset of proteinuria in women with hypertension alone in early pregnancy. Women with hypertension and proteinuria before 20 weeks of gestation exhibiting sudden increase in blood pressure, sudden increase in proteinuria, thrombocytopenia and increased liver enzymes.

CHRONIC HYPERTENSION

Hypertension present before pregnancy or first diagnosed before 20 weeks of gestation. Additionally, when gestational hypertension does not resolve after delivery, the condition is reclassified as chronic hypertension.

INCIDENCE AND RISK FACTORS

Incidences varies from 3 – 10 % in nulliparous women. In developing countries they rank second only to anaemia. A number of social, genetic, medical and obstetric conditions predispose to an increased risk of pre eclampsia.

RISK FACTORS

Extremes of age. (higher in teenage)

Nulliparity

Obesity BMI> 35 kg/m^2

Multifetal gestation

GHT – 13 versus 16% in singleton pregnancy

Pre eclampsia – 13 versus 5 % in singleton pregnancy.

Hydatidiform mole

Hydrops fetalis

Chronic hypertension.

Maternal diabetes.

Renal disorders.

Antiphospholipid syndrome

Systemic lupus erythematosus

Auto immune disorders

h/o smoking

abnormal uterine artery Doppler at 18 to 24 weeks.

Family h/o pre eclampsia (genetic)

Age :

Pre eclampsia commonly occurs at both extremes of reproductive age, but is greatest in women less than 20 years of age. White and African American women, 15- 17 years of age, were found to have 2.6-2.4 times risk respectively to develop pre-eclampsia compared to their 25-34 year old counterparts. Women who get pregnant after more than 10 years since the last pregnancy also have a greater risk.

Genetic factors :

In 1873, Elliot described the familial nature of the disease which was reviewed by Chesley in the year 1968. Elliot reported a patient who died of eclampsia. Her mother had a similar end, and four of her sister had eclampsia which proved fatal in three. There is a presence of increased susceptibility of the inherited genes from the pre eclamptic mother to the foetuses, which are capable of triggering pre eclampsia.

It is a multifactorial polygenic syndrome. Some of the genes responsible for this syndrome are

MTHFR gene affecting methylene tetra hydro folate reductase

Angiotensinogen gene(AGT)

Factor V(leiden) gene

HLA genes (various) causing immunological tolerance

NOS_3 (Glu 298Asp) gene affecting endothelial nitric oxide production

CTLA 4 cytotoxic T lymphocyte associated protein

LPL lipoprotein lipase

SERPINE 1 Serine peptidase inhibitor

F2 prothrombin(factor II) gene

ACE (Angiotensin converting enzyme) gene.

ETIOLOGY :

Inspite of various researches over years, the exact cause of pre eclampsia remains unclear. Gestational hypertension disorders occurs in women those

Are exposed to chorionic villi for first time

Are exposed to super abundance of chorionic villi , as in multiple pregnancy or molar pregnancy.

With pre existing condition of endothelial cell activation or inflammation such as diabetes or renal or cardiovascular disease.

Are genetically predisposed.

According to Sibai (2003), potential causes include the following

Abnormal invasion of trophoblast in the uterine vasculature.

Intolerance between maternal and fetoplacental tissues.(Immunological)

Maternal response to the cardiovascular changes of normal pregnancy.

Dietary deficiencies.

Genetic.

IMMUNOLOGICAL THEORY :

The possibility that immunological as well as the endocrine and genetic mechanisms are involved in genesis of pre eclampsia. The risk of pre-eclampsia is enhanced in the circumstances where, there is an impairment in the formation of antibodies to the sites of antigen on the placenta or where the number of antigens produced by the placenta is more when compared to antibody as in multiple pregnancy.

However some studies found no association of compliment factors c3, c3F with pre eclampsia.

GENETIC THEORY :

In the year 1979, Cooper and Liston revealed that the preeclamsia depends upon a single recessive gene, but multifactorial inheritance cannot be excluded.

DIETARY DEFICIENCY :

Some workers implicated that calcium deficiency might be one of the cause for pre eclampsia. Studies have reported that dietary supplements of 2gm of calcium per day after mid pregnancy reduce the incidence of preeclampsia.

ETIOPATHOGENESIS :

As Boyd stated pre eclampsia remains " die krankheit der theorien" the disease of theories. More accepted theories included abnormal trophoblast invasion of uterine blood vessels, changes in vasomotor activity, plasma volume and coagulation system. Their disturbances had been attributed to the endothelial cell activation or dysfunction and abnormal placentaion.

VASOSPASM :

The basic pathophysiology of pre eclampsia is vasospasm. Vasoconstriction causes resistance to blood flow and leads to the development of arterial hypertension.

ABSENCE OF SPIRAL ARTERIES REMODELLING :

"The inciting organ for development of pre eclampsia is placenta"

Uteroplacental vessels undergo two stages

First stage : before 12 weeks post fertilisation upto interface between the decidua and myometrium

Second stage : between 12 to 16 weeks. It involves invasion of intramyometrial segments of spiral arterioles.

Normally cytotrophoblasts of the developing placenta migrates through decidua and myometrium and invade the tunica media of the spiral arteries which supply blood to fetus. So these changes leads to transformation of small muscular arterioles to a large low resistence vessels. These changes occur at the end of first trimester and completed by 18 - 20 weeks of gestation.

But in preeclampsia , cytotrophoblasts fails to penetrate myometrial segment and so, the spiral arteries remains narrow and results in hypoperfusion of placenta which is the important component in preeclampsia pathogenesis. This placental ischemia causes maternal endothelial dysfunction.

In 1980, Dewolf and coworkers examined arterioles from the placental implantation site using electron microscopy and they found that in ealy stages there is damage of endothelial cells, accumulation of lipids in the myointimal cells resulting in narrow lumen.

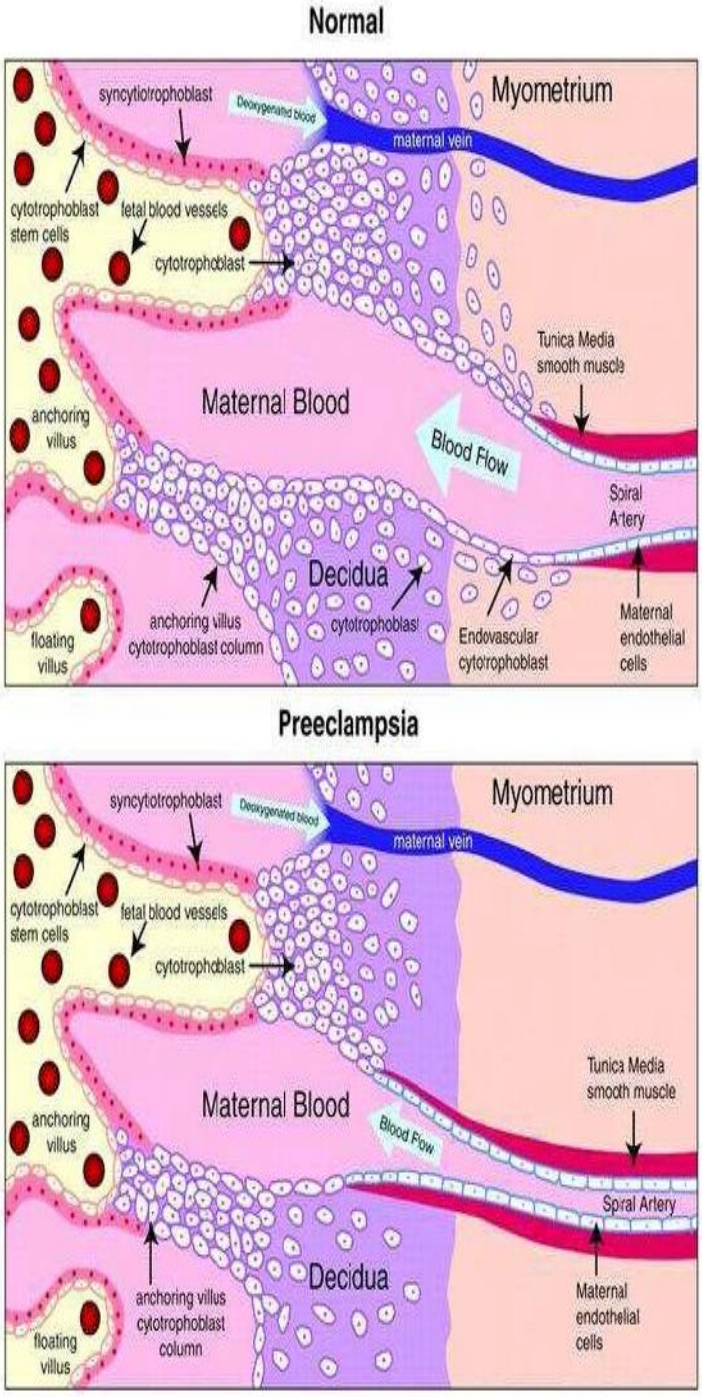


FIG 8: PATHOPHYSIOLOGY OF PRE ECLAMPSIA

IMMUNOLOGICAL INTOLERANCE

There was evidence to support that pre eclampsia is immune mediated. Immunologists explained that this condition where there is abnormality of the immune protective mechanism are shown to prevent the mother from rejecting fetuses. To support this concept , pre eclampsia is uncommon in patients who are immunosuppressed. From the early second trimester, women who are at risk of developing pre eclampsia had a significantly low number of T helper cells compared with normotensive pregnant women. Adenosine mediated Th1/Th2 imbalance, seem to be high in pre- eclamptic women in comparison to the normal pregnant women.

Placental changes in pre eclampsia have shown some similarity which is found in rejected kidney after transplantation.

" The evidence supporting this theory is that there may be a loss of maternal tolerance to paternally derived placental and fetal antigen".

Placenta has both paternal and maternal halotypes and genetic determinants. Compared to normal pregnant patients there is decreased level of messenger RNA for HLA-G in women with pre eclampsia.

Cytokines particularly the tissue necrosis factor(TNF α), interleukin 2 (IL2) and interleukin 6(IL6) are the mediators of immune maladaptation in pre eclampsia.

ENDOTHELIAL CELL ACTIVATION

If endothelium is intact, it will have anticoagulant property by releasing the nitric oxide and it blunts the vascular smooth muscle response to agonist. So endothelial cell damage release pro coagulants and there is decreased nitric oxide production and there is increased sensitivity to the pressors.

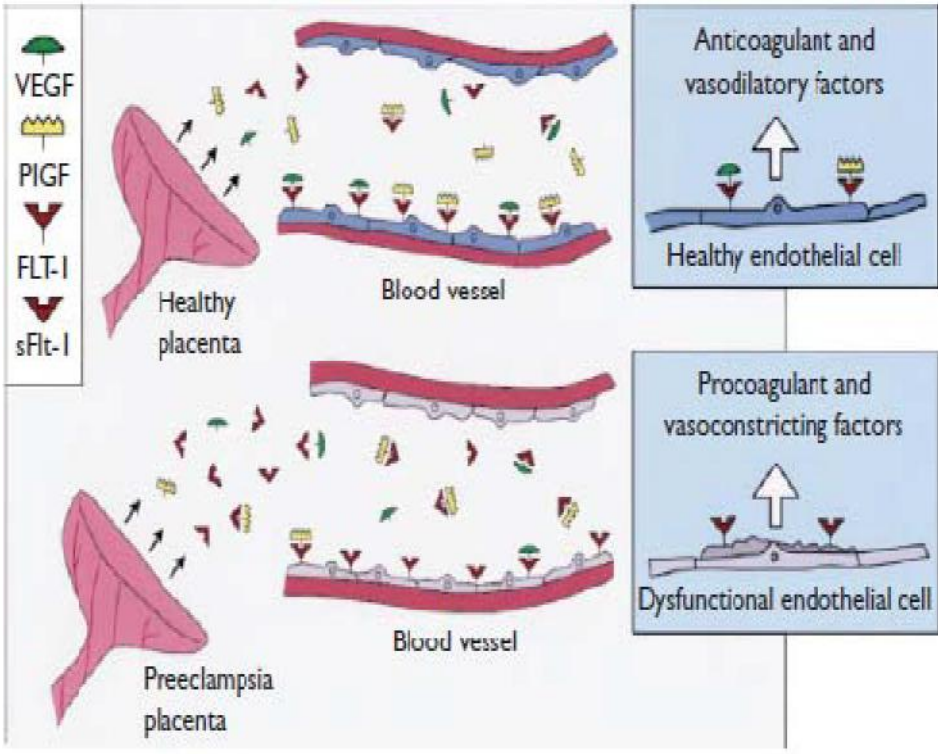


FIG 9: ENDOTHELIAL CELL ACTIVATION

PROSTAGLANDINS

Compared with normal pregnancy, production of endothelial prostacyclin (PGI2) is reduced in pre-eclampsia. Also there is an increased production of thromboxane A_2 by platelets, so the prostacyclin : thromboxane ratio is decreased.

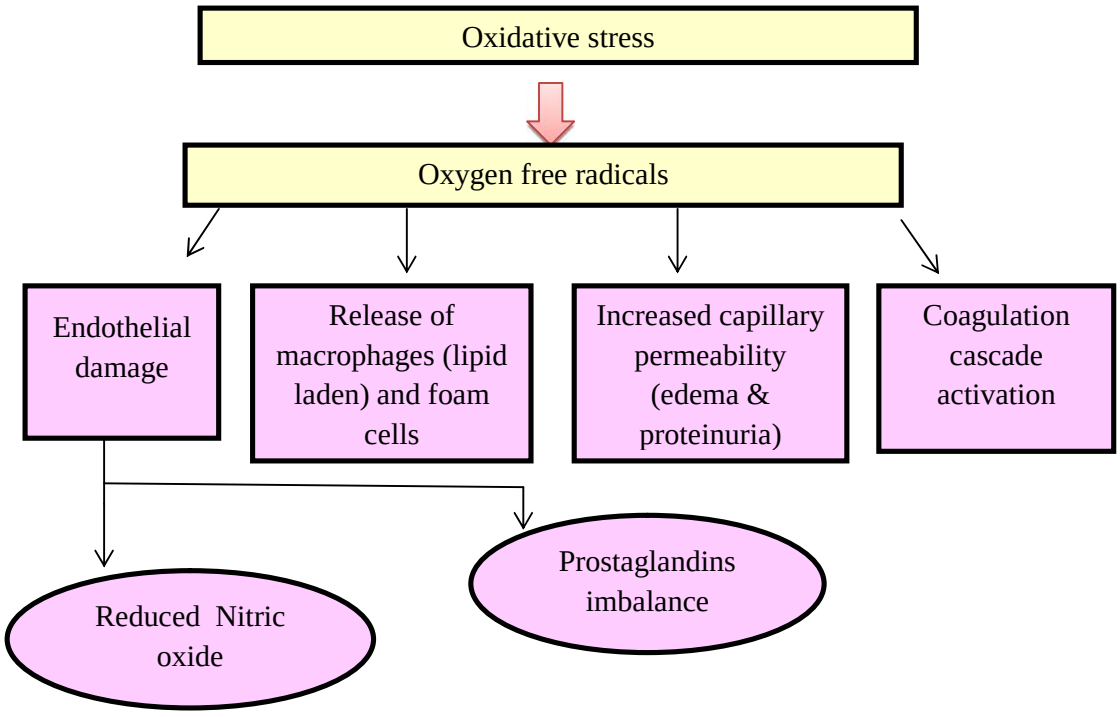
This leads to an increased response to vasopressor angiotensin II and finally leading to vasoconstriction.

NITRIC OXIDE

Nitric oxide, a potent vasodilator is produced by endothelial cells from L-Arginine. Reduced nitric-oxide synthesis in pre eclampsia increases mean arterial pressure and increases the sensitivity to vasopressor agents. The effect of nitric oxide production in pre eclampsia remains unclear.

OXIDATIVE STRESS

Pre eclampsia is due to activated leucocytes in the maternal circulation. Decidua contains a large group of cells which on activation releases noxious agents like the tumor necrosis factor- α, and leukotrienes which are responsible for the oxidative stress.



ENDOTHELINS

A potent vasoconstrictor produced by human endothelium. Endothelin levels are increased in pre eclamptic women compared with normal women. Some report shows that the magnesium sulphate decreases the endothelin I concentration.

ANGIOGENIC AND ANTI ANGIOGENIC PROTEINS

Balanced production of angiogenic and anti angiogenic factors are responsible for normal development of placenta.

In pre eclampsia, there is increased production of antiangiogenic factors resulting in endothelial dysfunction. New Researches currently use antiangiogenic proteins in prediction and diagnosis of pre eclampsia.

Two antiangiogenic proteins that increased in maternal circulation are :

Soluble endoglin:

It is 65 kDa molecule derived from placenta which inhibits TGF-β isotopes from binding with endothelial receptors, which decreases the nitric oxide release from endothelium.

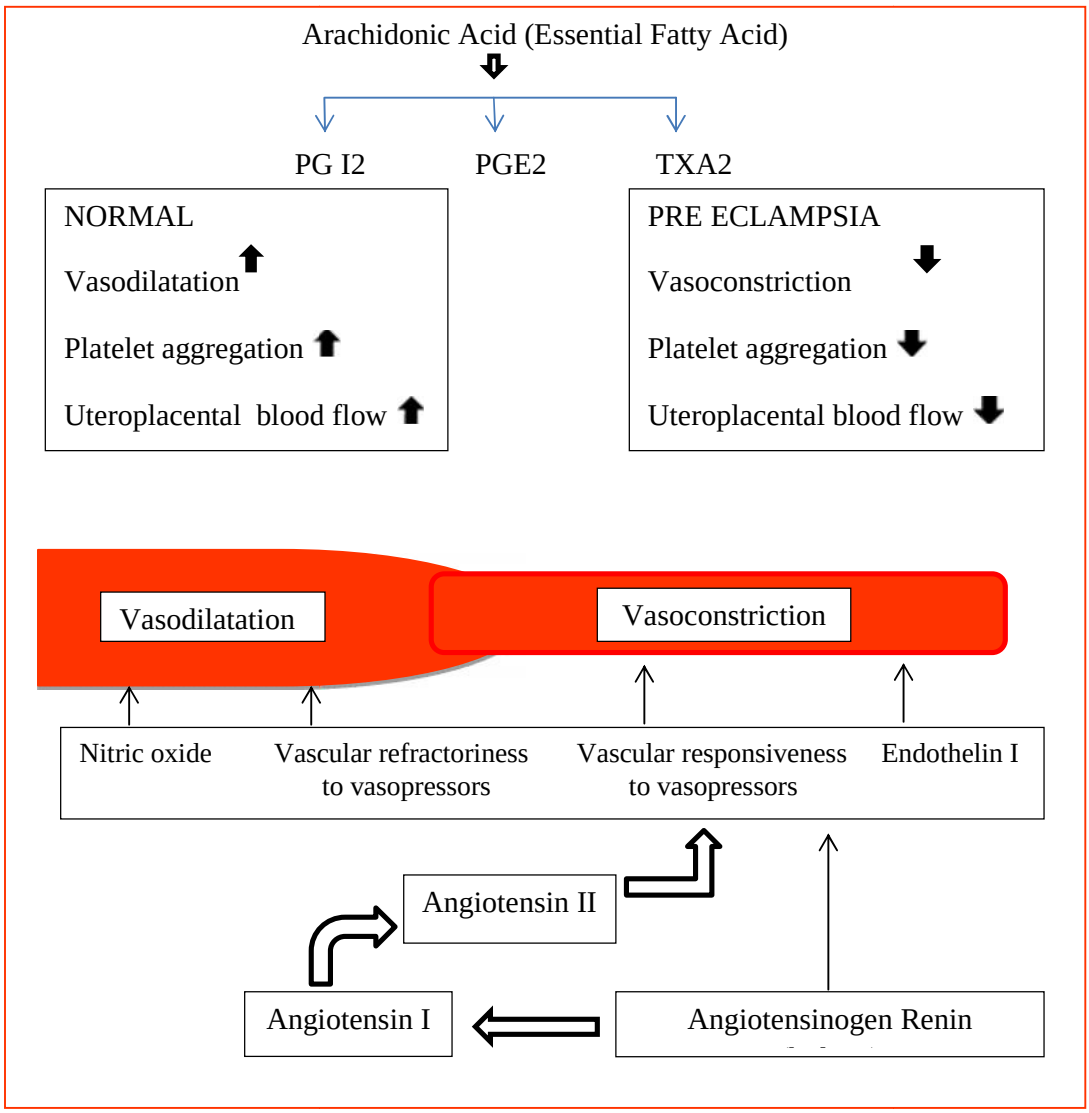
Soluble FMS like tyrosine kinase – 1 :

It decreases the placental endothelial growth factor and vascular endothelial growth factor, leading to endothelial dysfunction.

Both of these antiangiogenic factors begins to rise in maternal serum before pre eclampsia develops .

Increased level of antiangiogenic factors in the second trimester is associated with increased risk for pre eclampsia which is produced by trophoblastic tissue , which enters in to the maternal circulation causing angiogenic imbalance.

PATHOPHYSIOLOGY OF PRE ECLAMPSIA



RETENTION OF SODIUM

There is an increased plasma volume , glomerular filtration rate and renal blood flow in normal pregnancy, but in pre eclamptic women, there is decreasein plasma volume, renal blood flow and glomerular filtration rate resulting in retention of sodium which increases the sensitivity of vasopressors in pre eclampsia.

All signs and symptoms of pre eclampsia are well explained by response to generalised endothelial dysfunction.

Increased vascular permeability leads to development of proteinuria and edema.

Disturbed vascular tone of the endothelial cells leads to hypertension.

Expression of the pro-coagulants leads to coagulaopathy.

Endothelial dysfunction in the vasculatures of brain, liver, kidney and placenta causes headache, seizures, epigastric pain, visual disturbances and fetal growth restriction

In severe pre eclampsia , angiotensin II causes vasoconstriction which leads to local hypoxia and causes haemorrhage & necrosis causing end organ damage.

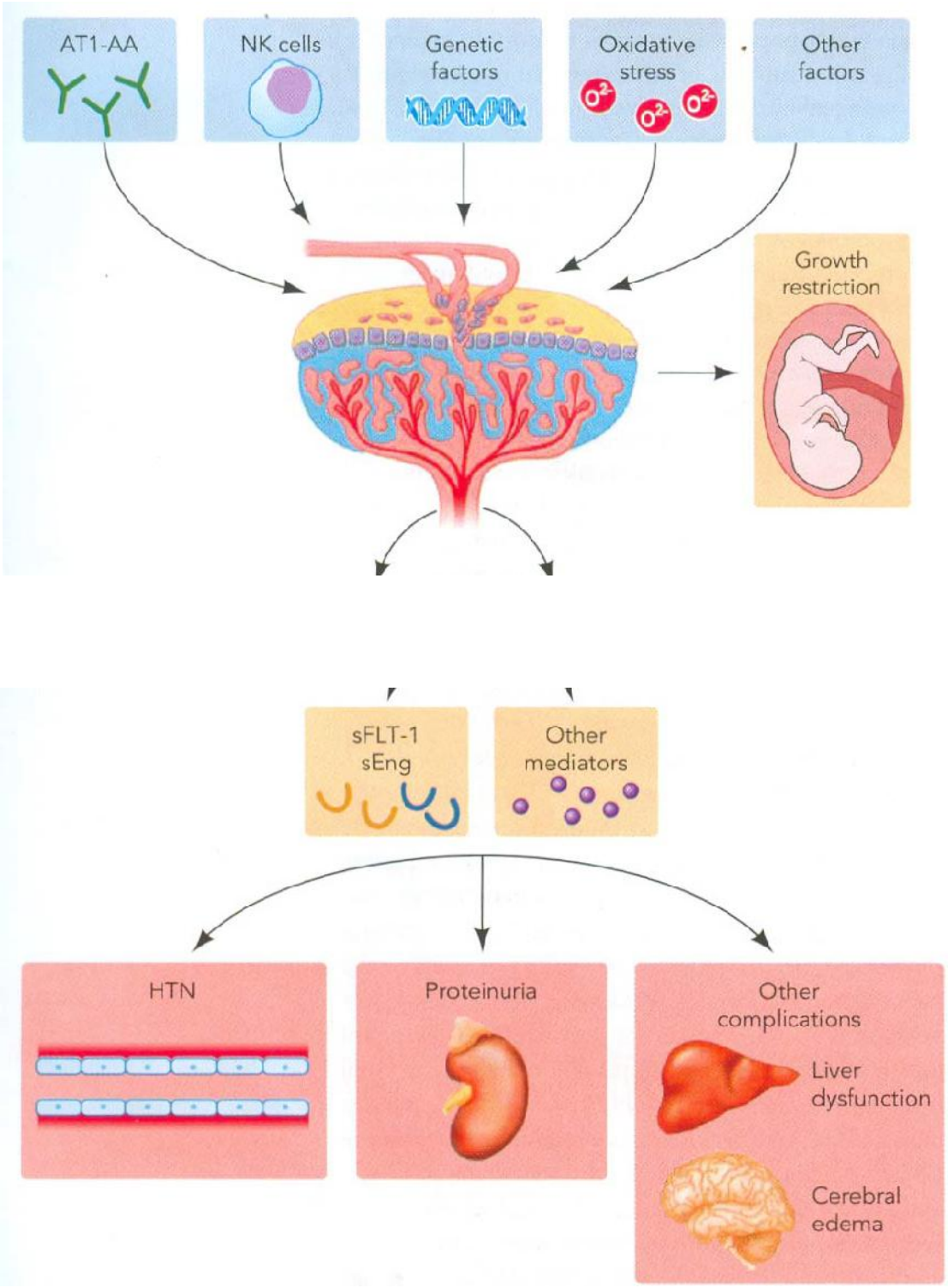


FIG 10: OVERVIEW OF PATHOPHYSIOLOGY

PATHOLOGICAL CHANGES

Pre eclampsia occurs in two stage.

Asymptomatic stage

Abnormal placental development during first trimester.

Placental insufficiency

Symptomatic stage

Hypertension, proteinuria.

CARDIO VASCULAR SYSTEM

Blood pressure = cardiac output X total peripheral resistance.

Normally cardiac output increases during pregnancy, but it rises further in pre eclampsia. Total peripheral resistance decreases during normal pregnancy whereas here it increases. This is the main cause of high blood pressure.

In pre eclampsia incidence of pulmonary edema is increased.

HEMATOLOGICAL SYSTEM

Normally, total blood volume increases because of the expansion of plasma leading to physiological anemia (hemo dilution)of pregnancy. This expansion in blood volume is reduced in gestational hypertension. Decreased regional perfusion in gestational hypertension resulting in hemoconcentration.

Contraction of intravascular space is associated with vasospasm and subsequent hemoconcentration. Haematocrit increases with increased severity of pre eclampsia. An attempt to expand the intravascular space by fluid therapy may increase pulmonary wedge pressure resulting in pulmonary edema because of capillary leak.

Main pathophysiology of pre eclampsia is vasospasm , which results in endothelial injury. This endothelial injury is responsible for microangiopathic hemolysis resulting in fragmentation of red blood cells, thrombocytopenia and anemia.

There is a low level of antithrombin III and high levels of fibronectin helping in diagnosis of pre eclampsia and it differentiates from chronic hypertension.

BLOOD AND COAGULATION

Among the haematological abnormality, thrombocytopenia is characteristic of pre eclampsia which may be life threatening.

Activation of platelets will lead to the endothelial dysfunction. Coagulation system is activated by tissue factor present in endothelium. This results in widespread disseminated intravascular coagulation(DIC).

THROMBOCYTOPENIA

Thrombocytopenia was described by Stancke in 1922, in patients with pre eclampsia. The platelet count is routinely done in all pre eclampsia patients.

Intensity of thrombocytopenia depends on the duration and severity of pre eclampsia. The platelet count < 1 lakh/µL indicates the severity. The platelet count decreases on the first day after delivery, then reaches the normal value in 4 to 5 days.

HELLP SYNDROME

It was first coined by Weinstein. It comprises of

Hemolysis

Elevated **L**iver enzymes

Low **P**latelet count

COAGULATION

Following are some of the abnormalities in pre eclampsia

Decreased levels of antithrombin III

Decreased plasma fibrinogen level

Decreased levels of Protein C and S

Increased levels of fibrin degradation products

Increased levels of fibrino peptides A & B

ENDOCRINE SYSTEM

Angiotensin II , catecholamine and vasopressin play an important role in high blood pressure and increased vascular resistance. Vascular sensitivity to

angiotensin II occurs 8 to 12 weeks prior to the onset of clinical symptoms pre eclampsia.

Indomethacin and aspirin are prostaglandin inhibitors which decreases the vascular sensitivity to angiotensin II.

RENAL SYSTEM

There is a reduction in renal perfusion and glomerular filtration rate due to increased resistance of renal afferent arterioles. Glomerular endotheliosis occurs blocking the filtration barrier. Sodium concentration in urine is increased. Fractional excretion of sodium urine osmolality and urine plasma creatinine ratio is an indication of pre renal involvement.

Serum uric acid concentration is elevated in pre eclampsia due to reduction in glomerular filtration rate and increased tubular reabsorption. In pre eclampsia there is decreased urinary excretion of calcium occurs.

RENIN – ANGIOTENSIN – ALDOSTERONE SYSTEM

It is responsible for the maintainence of norrmal blood pressure, sodium and blood volume status. Normally, plasma renin concentration and its activity, angiotensinII and aldosterone levels are increased and reduced refractoriness to angiotensin II effects.

But in pre eclampsia, there is a loss of refactoriness to angiotensin II effect which is demonstrated as early as 18 to 22 weeks of gestation .

LIVER

Commonly found pathological lesion in liver is periportal haemorrhagic necrosis. It manifest as epigastric pain and tenderness associated with elevation of liver enzymes alanine transferase and aspartate transferase.

Elevation of liver enzymes without symptoms are considered as markers of severe pre eclampsia. They ususally become normal within 3 days of delivery. Sometimes preeclampsia is confused with acute fatty liver of pregnancy, because it is also associated with hypertension, thrombocytopenia and elevated liver enzymes.

Brain

Brain involvement in pre eclampsia was first described from the autopsy specimens. But CT, MRI and Doppler studies gives much more important information of cerebrovascular system. Multiple petechial haemorrhages or larger haemorrhage in cortex, pons or midbrain. Intracerebral haemorrhage is seen in 60 % of eclampsia and is fatal in 30% of eclampsia..

Haemorrhage in basal ganglia, sub cortical edema, multiple non haemorrhagic areas of softening are also seen. Microscopic appearance of vascular lesions includes perivascular microinfarcts, haemorrhages and fibrinoid necrosis of arteriolar walls.

There are two theories to explain the cerebral involvement in women with eclampsia.

The first theory explains that vasospasm in cerebrovascular system based on angiographic images of diffuse or focal segmental narrowing of vessels. Diminished cerebral blood flow results in ischemia, infarction and edema.

The second theory is that if there is a sudden elevation of blood pressure it may exceed the normal auto regulatory capacity.

There is a disruption in end capillary pressure resulting in vasogenic edema because of increased hydrostatic pressure, extravastation of plasma and red cells through tight junctional opening.

VISUAL CHANGES

Diplopia , blurring of vision and scotoma occurs. Blindness is less common and it is reversible. Blindness from retinal lesion is caused either by serous retinal detachment or by retinal infarction which is termed Purtcsher retinopathy. Occasionally it accompanies with cortical edema. Eclampsia induced visual disturbances is an reversible condition.

UTEROPLACENTAL PERFUSION

Vasospasm results in decreased uteroplacental perfusion which is important in the pathogenesis of pre eclampsia. Previously studies were done to access the uteroplacental perfusion by peak systolic : diastolic velocity ratios from uterine and umblical arteries in women with pre eclampsia.

COMPLICATIONS

Maternal :

CENTRAL NERVOUS SYSTEM

Eclampsia

Cerebrovascular accident

Intracerebral haemorrhage or occasionally intracranial aneurysmal rupture.

Retinal detachment

Cortical blindness

RESPIRATORY SYSTEM

Pulmonary edema with or without left ventricular failure. It develops in 2.9% of pregnancies complicated by pre eclampsia.

Acute respiratory distress syndrome

RENAL SYSTEM

Renal cortical necrosis

Renal tubular necrosis

Renal failure - characterised by marked reduction in the glomerular filtration which leads to increased retention of urea, electrolytes and acid base abnormalities.

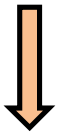
LIVER

HELLP syndrome

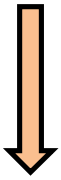
Hepatic rupture

It is one of the most severe consequences of pre eclampsia. It occurs more commonly in the elderly women in their first pregnancy.

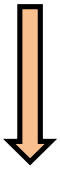
Endothelial dysfunction + intravascular fibrin deposits



Hepatic sinusoidal obstruction



Increase in intrahepatic vascular congestion and pressure and
Distortion of Glisson's capsule



Development of subcapsular hepatic hematoma and liver rupture

Fatty liver

HAEMATOLOGICAL - Disseminated intravascular coagulation (DIC)

Characterised by increase in fibrinolysis and fibrin formation leading to consumption of clotting factors, presenting as bleeding diathesis. Severe pre eclampsia is the most common cause of disseminated intravascular coagulation.

PLACENTA abruption placenta

Fetal :

"Preeclampsia is considered to be the maternal disorder in which fetus is an incidental participant, but from the fetus point of view , it is the fetal disorder and mother is an incidental participant."

In normal singletons, pre eclampsia is the major cause of intra uterine growth restriction. It indicates early onset severe disease. Because of diminished utero-placental blood flow, there is anoxia leading to liberation of thromboplastic substances from placenta which initiates intravascular coagulation.

There is

Increased secretion of chorionic gonadotropin

Increased secretion of steroid hormones

Deterioration of transport mechanism of vital aminoacids .

All of the above factors contributes to fetal hypoxia and IUGR of fetus.

Intra uterine fetal growth restriction(IUGR)

Intrauterine death (IUD)

Prematurity more likely to be iatrogenic in pre eclampsia

PREDICTION AND PREVENTION OF PRE ECLAMPSIA

Many attempts were made to find the early markers of impaired placenta perfusion, endothelial cell activation and dysfunction and faulty placentation. There is no valid screening test to predict pre eclampsia .

In year 2009, Conde-Agudelo and associates provided the review for the tests.

Placental perfusion/ vascular resistance :

Roll over test

Isometric handgrip or cold pressor test

Angiotensin II infusion

Mid trimester mean arterial pressure

Platelet angiotensin II binding

Renin

24- hour ambulatory blood pressure monitoring

Uterine artery doppler

Fetal Doppler velocimetry.

Fetal placental unit endocrine dysfunction

Human chorionic gonadotropin(hCG)

Alpha feto protein (AFP)

Estriol

Pregnancy associated protein A (PAAP A)

Inhibin A

Activin A

Placental protein 13

Corticotropin releasing hormone

Renal dysfunction

Serum uric acid

Microalbuminuria

Urinary calcium or kallikrein

Microtransferrinuria

N-acetyl- β-glucosaminidase.

Endothelial dysfunction/ oxidant stress

Platelet count and activation

Fibronectin

Endothelial adhesion molecule

Prostaglandins &Thromboxane

c-reactive protein & cytokines

endothelins&neurokinins B

VEGF, PlGF,PAI.

Leptin& p-selectin

Endoglin

Miscellaneous

Anti thrombin III

β_2 microglobulin

Atrial Natriuretic Peptides

Uterine artery Doppler

Non pregnant women

Reduced diastolic flow and notching of the uterine artery

Normal pregnancy

Due to the trophoblastic invasion, the notch disappears and flow increases.

"IF THERE IS PERSISTENCE OF A DIASTOLIC NOTCH IN THE UTERINE ARTERY OR INCREASED RESISTANCE AT 20 -22 WEEKS- it indicates second stage of trophoblastic invasion has not occurred"

This helps in the prediction of pre eclampsia and IUGR. In general, the uterine Doppler test is best among all the above test as there is no other test that are truly predictive. The latest combination method in first trimester include the

prediction of pre eclampsia is uterine artery Doppler along with pregnancy associated plasma protein(PAPP- A) and placental protein 13.

METHODS OF PREVENTION

Low salt diet

Salt restriction was earliest research efforts to prevent pre eclampsia(De snoo 1937). In 1998, knuist and collegue reported that salt restricted diet was not effective in prevention of pre eclampsia.

Calcium supplementation

In the 1980's(Belizan and vilar) studies were shown that patients with intake of low dietary calcium had increased the risk of pre-eclampsia .

Various studies (Levine and collegues) shows that unless the women has calcium deficiency, calcium supplementation has no effects on reducing pre eclampsia .

Fish oil supplementation

Eicosapentanoicacid and alpha linoleic acid are the most common dietary source of fish oil. It might prevent inflammatory mediated atherogenesis. But randomised trials (Makrides 2006, olafsdottir 2006, olsen 2000, and their collegues)shown that there is no such benefits.

Antioxidants

Vitamin C & vitamin E are naturally occurring anti oxidants which are reduced in pre eclampsia.(Raijmakers and associates 2004).

Thus supplementation of anti oxidants improves the oxidative property of women who are at risk of pre eclampsia. But (Poston 2006, Rumbold 2006) studies revealed that eclampsia has not reduced by the use of antioxidants.

Antithrombotic agents

Low dose aspirin

Wallenburg and associates 1986 studied that daily oral dose of 50 to 150 mg aspirin inhibits thromboxane A_2 synthesis. Paris collaborative group performed a meta analysis which showed that the relative risk of pre eclampsia was reduced by 10%.

Low dose aspirin + heparin

High incidence of thrombotic lesion in the placenta was found in severe pre eclampsia. In the year 2006, sergis and associates analysed the effect of prophylaxis with low dose aspirin and low molecular heparin with history of early onset pre eclampsia and low birth weight babies. They reported that there is a better pregnancy outcome in patients with low dose aspirin plus low molecular heparin than those with low dose aspirin alone.

Physical principles of Doppler Ultrasonography:

Doppler effect:

"Observed changes in the frequency of the energy wave transmission when relative motion occurs betweenthe source of wave transmission and observer". This change in frequency is called Doppler frequency shift/Doppler shift.

fd = ft-fr where fd - Doppler shift frequency

ft - transmittedfrequency

fr - receivedfrequency

Wave length decreases and the frequency increases, when the observer and the source move close to each other. Also, wavelength increases and frequency decreases when the observer and the source move away from each other. All forms of wave propagation applies this principle. The frequency shift is proportional to speed of movement. This principle is used in the Doppler effect.".

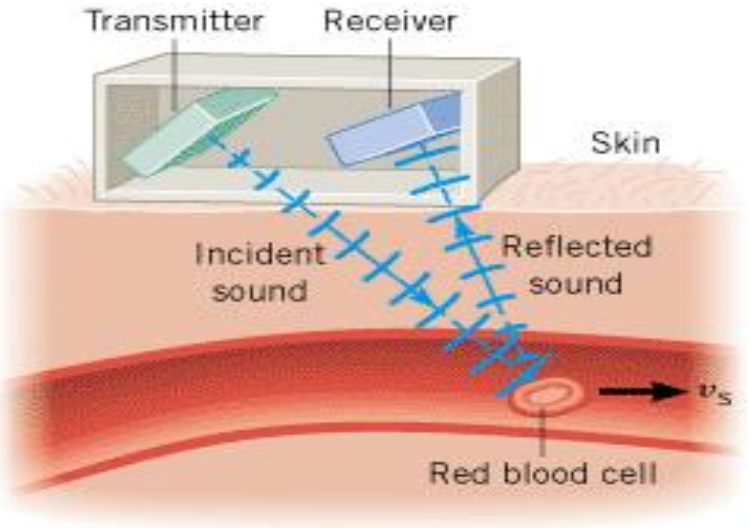


FIG 11: DOPPLER EFFECT

Doppler ultrasound:

"Even when an ultrasound beam encounters the blood flow, the principle of Doppler effect is seen. The moving targets within the blood circulation are millions of erythrocytes. This moving sources forms the basis of Doppler equation.

fd = 2 ft V/C, fd - Doppler frequency shift,

ft - frequency of incident beam (transducersfrequency)

V - velocity of scatterer in a given direction

C - propogation speed of sound in medium

When direction of incident beam is at an angle to direction of blood flow, the v in above equation is substituted by component of velocity in direction of the flow (obtained by cos Θ)

fd = 2 ft cos V/cosΘ

To find velocity,

V = fd c/2ft cos Θ

The equation above is the basis in clinical application of Doppler principle".

High pass and low pass filtering:

Two kinds of filters in use are

1. High pass filter

2. Low pass filter

High pass filter system eliminates the external low frequency component of Doppler signal, that arise from vessel wall. This should be used with caution as high setting eliminates end diastolic frequency shift from umbilical or uteroplacental circulation.

Technical considerations:

Four types of devices used to obtain Doppler signals are

Continuous wave Doppler:

Is relatively inexpensive machine which has two crystals. Of which one send high frequency and other receives signals continuously. It has the advantage to record high frequencies with low power output. But it is non selective and recognise all the signals in its way. The disadvantage is that it does not allow the visualisation of blood vessels of interest. It is useful to detect heart movements or even umbilical artery pulsations.

Pulsed Doppler:

By contrast, pulsed Doppler ultrasound is used to assess the flow velocity patterns within arteries and veins that are simultaneously visualised by gray scale ultrasound. Pulsed Doppler gate size , pulsed repetition frequency(PRF), angle of insonation and the gray scale imaging can be adjusted to obtain pure waveforms of high quality.

In general, blood flow velocities in the placental and fetal circulations ranges between 10 to 80 cm/sec. Pulsed Doppler is thus particularly helpful in obtaining

reliable uterine artery Doppler wave forms and is essential in assessing the various parts of the fetal circulation.

Colour flow Doppler:

Colour flow Doppler is an extension of the pulsed Doppler in that colour signal is assigned to direction of flow, by convention, red flow towards probe and blue flows away from it. Colour flow Doppler, therefore, detects the blood flow velocity in the same plane as the ultrasound probe.

Low angles of insonation are required in order that flow may be visulaised in various vessels. Flow is best observed at the appropriate PRF settings. Otherwise no flow may be detected or a multitude of low flow vessels will obscure the vessels of interest.

Power Doppler:

Recent technical development that detects the blood flow velocity independant of angle of insonation. This method of imaging is particularly useful in assessing the areas of high blood flow velocity and delineating the vascular from non vascular areas.

Wave form analysis:

Quantitative analysis:

The Doppler output results in flow velocity wave form (FVW) representing the velocity envelope through cardiac cycle. There are three common methods of describing peak blood flow velocity wave forms.

Systolic / Diastolic (S/D) ratio : $\frac{\text{Peak systolic velocity}}{\text{End diastolic velocity}}$

Pulsatility Index (PI) : $\frac{\text{Peak systolic- End diastolic velocity}}{\text{Mean velocity}}$

= A-B/M

Resistance Index (RI) : $\frac{\text{Peak systolic- End Diastolic Velocity}}{\text{Peak systolic velocity}}$

= A-B/A

A = Peak systolic velocity

B = End diastolic velocity

C = Early diastolic velocity

M = Mean velocity

S/D ratio gives a simple evaluation of the blood flow during diastole and provides estimation of the down stream resistance.

Pulsatility index is considered as the mean velocity diameter (ie) the whole flow is given consideration, not just the diastolic flow and hence can be used to analyse the data from various vessels without encountering the excessive variation that can be caused by the duration by small numbers as with other indices.

The pourcelot index or RI is useful when the diastolic flow is absent or reversed and when S/D cannot be calculated. It helps in comparing any waveform irrespective of its diastolic flow.

Qualitative Analysis :

Qualitative or descriptive methods may be used to describe the wave forms in uterine, umbilical or middle cerebral artery circulation.

An abnormal uterine artery waveform may be described either by the presence or absence of an early diastolic notch or by the PI.

Umbilical and middle cerebral artery Doppler waveforms may be described as normal with reduced diastolic flow, absent end diastolic flow (EDF) or reversed EDF.

Uterine Artery :

In first trimester of pregnancy, trophoblast invade the uterine vessel and result in dilated spiral arteries, which increases uterine perfusion from 10 fold to 12 fold.

Uterine arterial blood flow in a non pregnant women is 50 ml/min and increases to over 700ml/min in third trimester of pregnancy and thus the diastolic component of the uterine artery Doppler is transformed during normal pregnancy from one of low peak flow velocity and early diastolic notch to one of the high flow velocity and absence of early diastolic notch by 18-22 weeks.

Uterine artery waveform by the mid –second trimester is therefore characterised by the high end diastolic velocity with continuous forward blood flow throughout the diastole. In late gestation, the end diastolic flow typically raises. Indices that quantify the above waveforms include Pulsatality Index, Resistance Index and notching of uterine arteries.

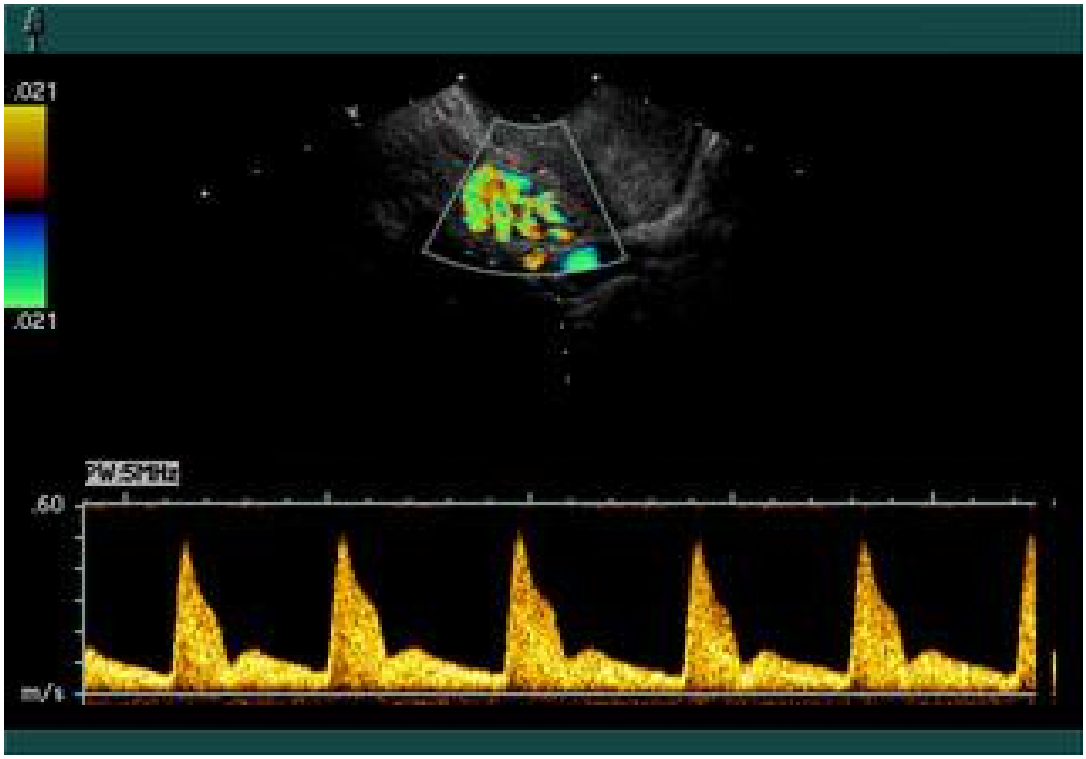


FIG 12: UTERINE ARTERY EARLY DIASTOLIC NOTCH

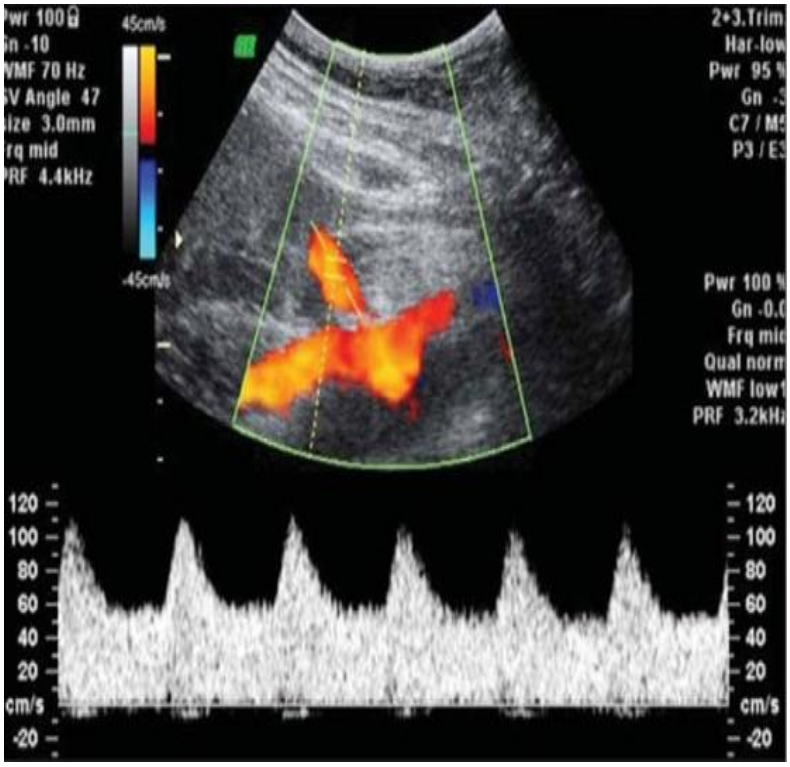


FIG 13: NORMAL UTERINE ARTERY DOPPLER

However failure of normal endovascular trophoblastic invasion of spiral arteries resuts in the increased uterine artery vascular resistance and decreased perfusion of placenta. With extreme degree of placental dysfunction, diastolic blood flow can be absent or reversed.

A recent literature review reported that the abnormal uterine artery waveforms are better predictor of preeclampsia than of IUGR when performed after 16 weeks of gestation. An abnormal PI and uterine artery notching in the second trimester best predicted preeclampsia.

Indication for assessing uterine vessel Doppler USG are

Previous h/o preeclampsia.

Previous IUGR.

Elevated maternal serum AFP.

High hcg levels

Because of high negative predictive value, patient will not develop pre eclampsia if PI is normal in both uterine vessel. If one vessel is abnormal, patient is advised to have frequent ANC visits.

Umbilical Artery:

The Umbilical artery Doppler denotes the presence / absence of the resistance of placental bed to blood flow between fetus and placenta. It strongly co relates with the acid-base balance of fetus. This measurement is Umbilical artery

S/D ratio. The PI has the advantage of producing a numerical value when diastolic flow is absent.

UMBILICAL ARTERY NORMAL DOPPLER

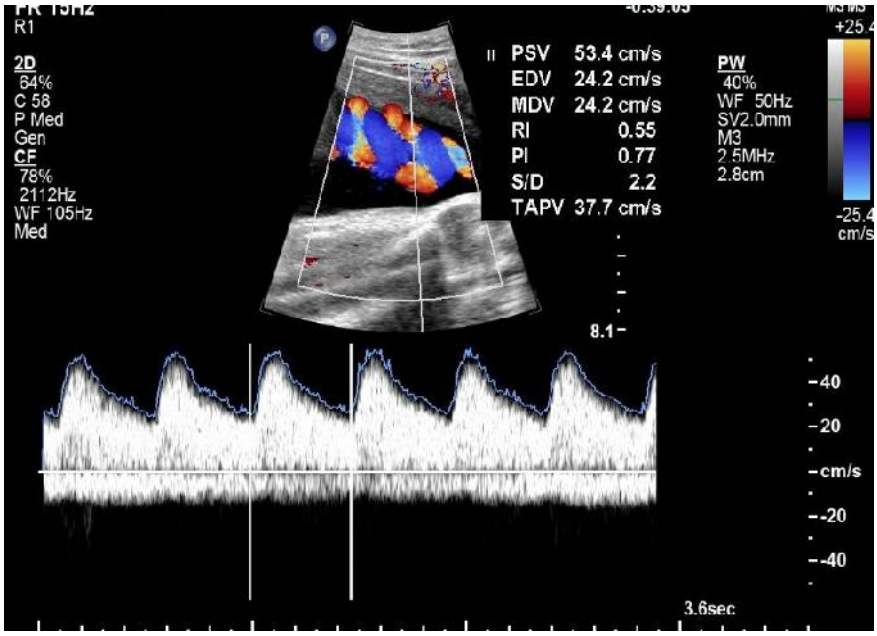


FIG 14: NORMAL UMBILICAL ARTERY DOPPLER

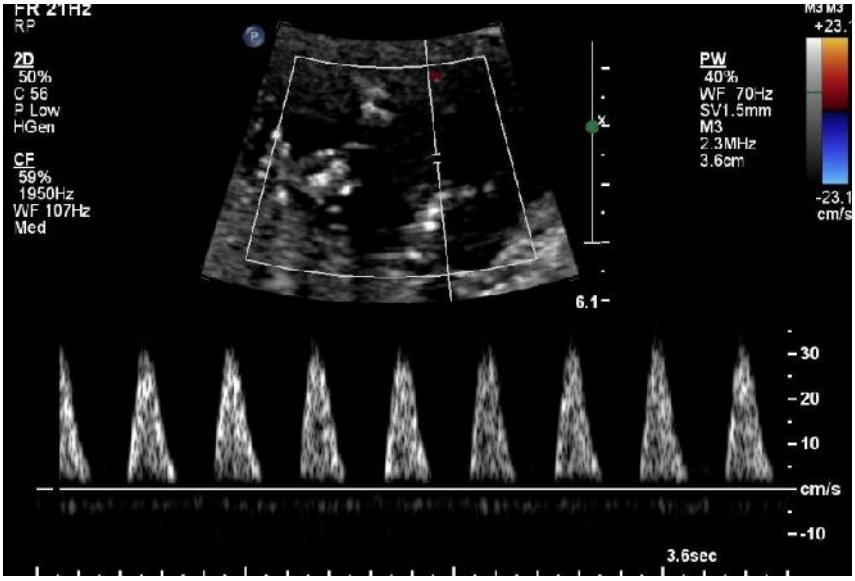


FIG 15: UMBILICAL ARTERY AEDF

TABLE 29

DOPPLER VALUES OF UMBILICAL VESSEL

GESTATION (weeks)	HYPERTENSIVE			NORMOTENSIVE		
	S/D	RI	PI	S/D	RI	PI
32 – 34	4.74 ± 1.78	0.94 ± 0.26	2.0 ± 0.82	2.92 ± 0.06	0.65 ± 0.02	1.1 ± 0.14
35 – 37	3.54 ± 0.97	0.78 ± 0.12	1.27 ± 0.32	2.36 ± 0.09	0.56 ± 0.03	0.77 ± 0.05
38 – 40	3.09 ± 0.76	0.72 ± 0.11	0.99 ± 0.23	2.23 ± 0.13	0.55 ± 0.02	0.74 ± 0.06

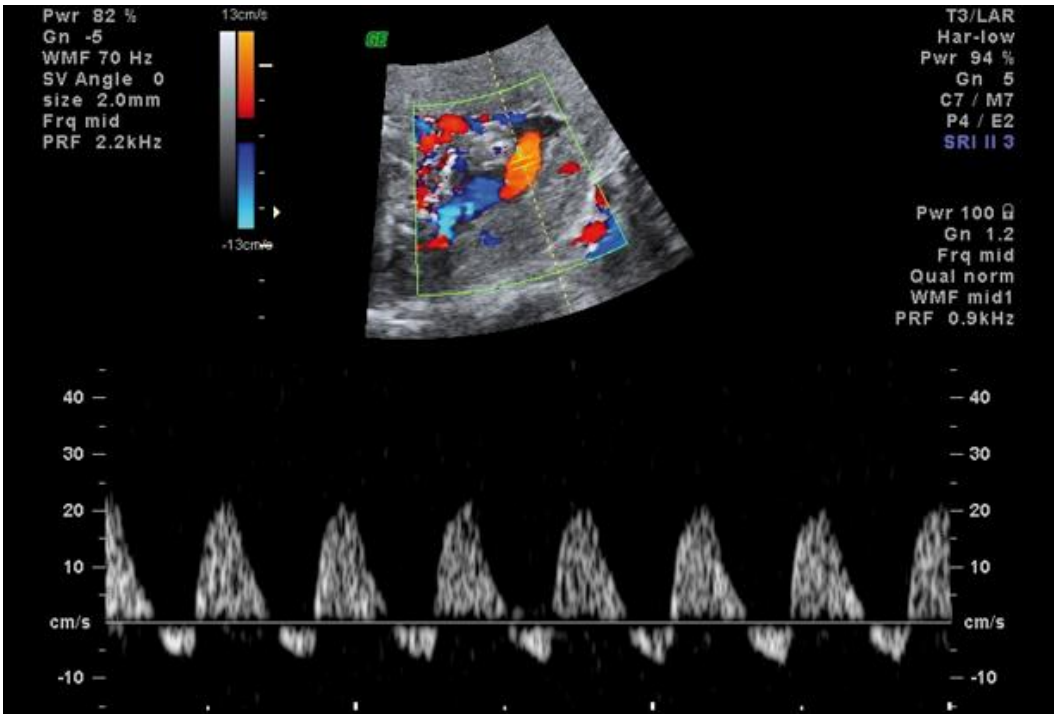


FIG 16: UMBILICAL ARTERY REDF

To obtain more consistent results , the UA S/D ratio should be obtained in the free loop of cord midway between the placental insertion, the site of less resistance and fetal insertion, the site of maximal resistance flow.

During the normal pregnancy, UA have low resistance demonstrated by the presence of abundant diastolic flow and reflected in low S/D ratios. During normal pregnancy there is a slow and continuous decline in the S/D ratio that reaches its lowest value after 36 weeks gestation.

When the pregnancy is complicated by the increased placental vascular insufficiency causing FGR, diastolic flow decreases causing UA S/D ratio to increase 2SD or higher above the mean for the gestational age. An increase in UA S/D ratio even if it is marked does not indicate fetal hypoxia. However, with progression of placental vascular insufficiency the UA waveforms will show ADF and finally reversed diastolic flow (RDF) which indicate the presence of fetal hypoxemia and the need to delivery of fetus.

Randomised clinical trials and meta analysis have demonstrated that the use of UA Doppler in high risk pregnancies results in approximately one third decrease in the perinatal mortality (Alfirevic and Neilson 1995; Divon 1996, Goffinet et al 1997).

Studies have also demonstrated the strong relationship between the results of UA velocimetry and the presence of fetal academia in blood sample obtained by cordocentesis (Vintzileous et al 1991; Yoon etal 1993)

Middle Cerebral Artery:

When placental vascular reistance increases above a certain threshold, the fetus develops a compensatory response, increasing the blood flow to vital organs such as the heart and brain and decreasing the blood flow to mesenteric, renal and peripheral circulation. The hemodynamic adaptation protects the integrity of the fetal brain in the face of diminished availability of nutrients and can be assessed by comparing the UA and MCA Doppler waveforms.

Under the normal conditions, the UA waveforms are characterised by abundant diastolic flow corresponding to a minimal reistance to flow in the fetal placental circulation. The MCA waveforms are completely different and show minimum or no diastolic flow

In the early stage of placental insufficiency, there is a decrease in Umbilical artery diastolic flow and increase in S/D ratio, resulting in a compensatory increase in brain circulation. This in turn results in increased diastolic blood flow and decreased MCA S/D ratio.

With the progression of placental insufficiency, the UA and MCA S/D ratios become similar and eventually the MiddleCerebralArtery S/D ratio will become smaller than the UmbilicalArtery S/D ratio. This is called Brain Sparing effect or centralisation of the flow.

Centralisation is signal that the fetus is under appreciable placental resistance to flow and inadequately compensating for this problem by improving the blood flow to the brain.

The MCA should be sampled near the origin from internal carotid artery. Reference values for MCA PI changes throughout the pregnancy. The lower PI values in early and late gestation may be caused by increased metabolic requirements of the brain during these periods. Several conditions are associated with an increase or decrease of the MCA PI when compared to the normal value.

Other Arteries:

Many other arteries like the descending aorta, splenic artery, superior mesenteric artery, adrenal artery, renal artery, femoral artery, internal and external iliac arteries have been studied.

Safety of Doppler ultrasound:

Equipments are regulated to be set for the lowest power settings sufficient to produce adequate images, known as the ALARA (As Low As Reasonably Achievable)

ALARA Principle:

The biological effect of high energy ultrasound includes heating and cavtitaion of tissues, teratogenicity and mutagenticity.

Cavitation :

It is caused by the vacuum following the ultrasound pulsed wave.

Heating:

It depends on USG intensity,duration of exposure and type of tissue. Neural tissue is particularly sensitive to hyperthermia.

Potential pitfalls :

Angle of insonation :

Common Doppler indices such as PI , RI and S/D ratio are not influenced by angle of insonation. However high angles of insonation will reduce the calculated peak velocity such that the proportion of the total waveforms attributable to background noise will become greater.

Wide angles of insonation can lead to apparent loss of diastolic frequencies leading to error in the diagnosis of placental vascular insufficiency.

Heart Rate :

An increase in the fetal heart rate will shorten the time for diastole and therefore lead to increased diastolic flow velocity.

Conversely, in complete heart block, a long diastolic phase will result in low diastolic velocities and high PI values.

SUMMARY

In this prospective study in a set up of tertiary level care, significance of Doppler indices abnormality and its perinatal outcome have been evaluated among preeclamptic patients.

In the study with uterine artery, 27% were found to have abnormal pattern, 27% with uterine artery high resistance and 28% showed uterine artery early diastolic notch in study group.

With the study of umbilical artery in the study group, 55% were found to have abnormal pattern, 56% with umbilical artery high resistance , 54% with absent end diastolic flow and 29% with reversed end diastolic flow.

17% were found to have abnormal middle cerebral artery pattern among the study group.

Cesarean section rate incidence was higher in the study group (43%) compared with the control group (17%).

Neonatal mortality accounted to 8% which is similar to Mikovic study et all.

CONCLUSION

200 Patients were taken for my study. Out of which 100 belong to control group and 100 were in study group.

In study group there is an increase in the doppler abnormality among all three major vessels which includes uterine artery, umbilical artery and middle cerebral artery.

Umbilical artery and middle cerebral artery doppler abnormality are a better indicator of perinatal outcome.

Those who have abnormal doppler velocimetry, there is an increased incidence of still birth and IUD when compared to control group.

Similarly one minute and five minute APGAR rate for those babies are low when compared to control group. And also the incidence of neonatal complications after birth is also increased with abnormal dopper velocimetry.

The incidence of caesarean section rate is increased among abnormal Doppler velocimetry.

Thus Doppler velocimetry is a major support for the conventional antepartum surveillance especially in pre eclampsia.

Abnormal doppler velocimetry alarms the obstetrician to plan the pregnancy in a tertiary care centre with a better NICU setup as it warrants effective monitoring of the patient and expert neonatal care.

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PROFORMA

Name: Husband name:

Age: Case no:

IP no.: Occupation:

Obs code: Date of admission:

LMP : Date of delivery:

EDD: Socio economic status:

Period of gestation:

Chief complaints:

History of presenting illness:

Menstrual history:

Marital history :

Obstetric history:

Past:

Present:

I trimester

II trimester

III trimester

Past history:

H/O similar illness

H/O hypertension

H/O diabetes/epilepsy/ thyroid disorder/ heart disease/ asthma

H/O renal or liver disease/ auto immune disorder

H/O chronic drug intake/ trauma

Family history:

GENERAL EXAMINATION:

Height:

Weight:

PR:

BP:

Breast:

Thyroid:

Spine:

Pedal Edema:

SYSTEMIC EXAMINATION:

CVS:

RS:

PA:

Inspection:

Palpation:

Auscultation:

Investigations:

Hb%

Blood grouping typing:

Blood sugar:

Serum urea:

Serum creatinine:

LFT:

Urine albumin:

Urine sugar:

Urine microscopic exam.:

USG OBS:

Singleton:

Viability:

GA:

Placenta:

Presentation:

AFI:

EFW:

Congenital Anomalies:

Doppler flow in Umbilical artery:

	S.D. Ratio	R.I	P.I.	Diastolic flow
Right				
Left				

Doppler flow in Middle cerebral artery:

	S.D. Ratio	R.I	P.I.	Diastolic flow
Right				
Left				

Doppler flow in Uterine artery:

	S.D. Ratio	R.I	P.I.	Diastolic flow
Right				
Left				

Maternal outcome:

Mode of delivery:

Vaginal:

Assisted vaginal:

LSCS: Ind:

Intra natal course and complication if any:

Fetal outcome:

Live birth/ Still birth/ IUD:

Term/ Preterm:

Male/ Female:

APGAR :

Weight of the baby:

HC of the baby:

IUGR:

Ponderal index:

Neonatal complication if any:

Placenta:

Colour of the liquor:

MASTER CHART SCALE

	1	2	3
AGE (years)	Less than 20	20 - 30	More than 30
PARITY	Primi	Multi	
UTERINE ARTERY			
A) Pattern	Normal	Abnormal	
B) High resistance flow	Absent	Present	
C) Early diastolic notch	Absent	Present	
UMBILICAL ARTERY			
A) Pattern	Normal	Abnormal	
B) High resistance	Absent	Present	
C) Absent end diastolic flow	Absent	Present	
D) Reversal of end diastolic flow	Absent	Present	
MIDDLE CEREBRAL ARTERY			
A) Pattern	Normal	Abnormal	
B) Increased diastolic flow	Absent	Present	
DELIVERY	Vaginal	Instrumental	LSCS
CONDITION	IUD	Stillbirth	Live birth
MATURITY	term	Preterm	
APGAR 1 MIN	≥7/10	5/10 – 6/10	≤4/10
APGAR 5 MIN	≥7/10	5/10 – 6/10	≤4/10
NNC	Death	Without complication	With complication

STUDY GROUP

S.NO	I.P. NO	AGE	PARITY	UTERINE ARTERY			UMBILICAL				MCA		DELIVERY	COND ON DELIVERY	MATURITY	APGAR 1MIN	APGAR 5 MIN	NNC
				PATTERN	HIGH RESI	E.D.N	PATTERN	HIGH RESI	AEDF	REDF	PATTERN	IDF						
1	7169	2	1	1	1	1	2	2	2	1	1	1	3	3	1	2	1	2
2	7148	2	1	2	2	2	2	2	2	2	2	2	3	3	1	2	2	3
3	71208	2	1	1	1	1	1	1	1	1	1	1	2	3	1	1	1	2
4	7223	2	1	1	1	1	2	2	2	1	1	1	3	3	1	2	1	2
5	7568	1	1	1	1	1	2	2	1	1	1	1	1	3	1	1	1	2
6	8117	2	1	1	1	1	2	2	2	2	1	1	3	3	1	3	2	3
7	8330	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
8	7998	2	1	1	1	1	2	2	2	2	2	2	3	3	2	3	2	3
9	9074	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
10	9234	2	1	1	1	1	2	2	2	1	1	1	1	3	1	1	1	2
11	9647	2	1	1	1	1	1	2	2	1	1	1	1	3	1	2	1	2
12	9879	2	1	2	2	2	2	2	2	2	2	2	3	3	2	2	2	1
13	10346	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
14	10239	2	1	1	1	1	2	2	2	1	1	1	1	3	1	2	1	2
15	10787	2	1	2	2	2	2	2	2	2	1	1	3	3	1	2	1	3
16	11237	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
17	11846	2	1	2	2	2	2	2	2	2	2	2	3	3	2	2	2	3
18	12076	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
19	12511	2	1	1	1	1	2	2	2	1	1	1	1	3	2	2	1	2
20	12277	2	1	1	1	1	2	2	2	2	1	1	3	3	1	1	1	2
21	12999	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
22	13112	2	1	1	1	1	2	2	2	1	1	1	1	3	1	2	1	2
23	13981	3	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
24	13746	2	1	2	2	2	2	2	2	2	2	2	1	1	2	3	3	1
25	14486	2	1	1	1	1	2	2	2	1	1	1	3	3	1	2	1	2
26	14703	2	1	2	2	2	2	2	2	2	1	1	3	3	2	2	2	3
27	14896	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
28	15301	2	1	2	2	2	2	2	2	2	2	2	3	3	2	2	2	1
29	15673	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
30	15871	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
31	16298	2	1	1	1	1	2	2	2	1	1	1	1	3	1	2	1	2
32	16906	1	1	2	2	2	2	2	2	2	1	1	3	3	2	2	2	3
33	17030	2	1	1	1	1	2	2	2	2	2	2	3	3	2	3	2	3
34	17740	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2

S.NO	I.P. NO	AGE	PARITY	UTERINE ARTERY			UMBILICAL				MCA		DELIVERY	COND ON DELIVERY	MATURITY	APGAR 1MIN	APGAR 5 MIN	NNC
				PATTERN	HIGH RESI	E.D.N	PATTERN	HIGH RESI	AEDF	REDF	PATTERN	IDF						
35	17871	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
36	18901	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
37	18534	2	1	1	1	1	2	2	2	1	1	1	1	3	1	2	1	2
38	18739	1	1	2	2	2	2	2	2	2	2	2	3	3	2	3	2	1
39	19478	2	1	1	1	1	2	2	2	1	1	1	3	3	1	2	1	2
40	19978	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
41	20278	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
42	20987	2	1	1	1	1	2	2	2	1	1	1	3	3	1	2	1	2
43	20411	1	1	2	2	2	2	2	2	2	1	1	3	3	1	2	2	3
44	21009	2	1	2	2	2	2	2	2	2	1	1	3	3	2	2	2	3
45	21986	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
46	22010	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
47	22876	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
48	23007	2	1	1	1	1	2	2	2	1	1	1	3	3	1	1	1	2
49	23497	2	1	2	2	2	2	2	2	2	2	2	1	1	2	3	3	1
50	23567	2	1	1	1	1	2	2	2	1	1	1	1	3	1	2	1	2
51	24111	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
52	24998	2	1	1	1	1	2	2	2	1	1	1	3	3	1	2	1	2
53	25789	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
54	25376	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
55	25972	2	1	1	1	1	2	2	2	1	1	1	3	3	1	2	1	2
56	26746	2	1	2	2	2	2	2	2	2	1	1	3	3	1	2	2	3
57	26431	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
58	27128	3	1	1	1	1	1	1	1	1	1	1	1	3	1	2	1	2
59	27340	2	1	2	2	2	2	2	2	2	1	1	3	3	1	2	2	3
60	27870	2	1	1	1	1	2	2	2	1	1	1	3	3	1	2	1	2
61	28543	2	1	1	1	1	2	2	2	1	1	1	3	3	1	2	1	2
62	28289	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
63	29012	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
64	29478	2	1	1	1	1	2	2	1	1	1	1	1	3	1	2	1	2
65	29843	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
66	30236	2	1	2	2	2	2	2	2	1	1	1	3	3	1	2	1	2
67	30012	2	1	2	2	2	2	2	2	2	2	2	3	3	2	3	2	3
68	29568	2	1	1	1	1	2	2	2	2	1	1	3	3	1	2	1	2
69	29238	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
70	30446	2	1	2	2	2	2	2	2	2	2	2	1	1	2	3	3	1

S.NO	I.P. NO	AGE	PARITY	UTERINE ARTERY			UMBILICAL				MCA		DELIVERY	COND ON DELIVERY	MATURITY	APGAR 1MIN	APGAR 5 MIN	NNC
				PATTERN	HIGH RESI	E.D.N	PATTERN	HIGH RESI	AEDF	REDF	PATTERN	IDF						
71	30786	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
72	30989	2	1	1	1	1	2	2	2	1	1	1	3	3	1	2	1	2
73	30886	2	1	2	2	2	2	2	2	2	2	2	3	2	2	3	3	1
74	30647	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
75	31478	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
76	31198	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
77	31374	2	1	1	1	1	2	2	2	1	1	1	3	3	1	1	1	2
78	31621	2	1	2	2	2	2	2	2	2	2	2	3	3	2	3	2	3
79	31945	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
80	32128	2	1	2	2	2	2	2	2	2	1	1	3	3	1	2	2	3
81	32377	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
82	32546	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
83	32647	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
84	32978	2	1	2	2	2	2	2	2	1	1	1	3	3	1	2	1	2
85	33768	2	1	1	1	1	2	2	2	2	2	2	3	2	2	3	3	1
86	33236	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
87	33576	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
88	33898	2	1	2	2	2	2	2	2	2	1	1	3	3	1	3	2	3
89	33976	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
90	34121	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
91	34591	1	1	2	2	2	2	2	2	2	2	2	1	1	2	3	3	1
92	34999	2	1	2	2	2	2	2	2	1	1	1	3	3	1	2	1	2
93	34784	2	1	2	2	2	2	2	2	1	1	1	3	3	1	2	1	2
94	34437	2	1	1	1	2	2	2	2	1	1	1	3	3	1	2	1	2
95	35730	2	1	2	2	2	2	2	2	2	1	1	3	3	2	3	2	3
96	35227	2	1	2	2	2	2	2	2	2	2	2	3	3	2	3	2	3
97	35189	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
98	36440	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
99	36101	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
100	36841	2	1	1	1	1	1	1	1	1	2	2	1	3	1	1	1	2

CONTROL GROUP

S.NO	I.P. NO	AGE	PARITY	UTERINE ARTERY			UMBILICAL				MCA		DELIVERY	COND ON DELIVERY	MATURITY	APGAR 1MIN	APGAR 5 MIN	NNC
				PATTERN	HIGH RESI	E.D.N	PATTERN	HIGH RESI	AEDF	REDF	PATTERN	IDF						
1	7251	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
2	7133	1	1	1	1	1	1	1	1	1	1	1	2	3	1	1	1	2
3	7122	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
4	7168	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
5	6956	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
6	7892	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
7	8447	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
8	8170	2	1	1	1	1	1	1	1	1	1	1	1	3	2	2	1	2
9	8798	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
10	8609	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
11	9476	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
12	10010	2	1	1	1	1	1	1	1	1	1	1	1	2	1	3	3	1
13	10127	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
14	10567	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
15	11011	1	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
16	11512	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
17	11348	2	1	1	1	1	1	1	1	1	1	1	2	3	1	1	1	2
18	11986	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
19	12121	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
20	12378	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
21	12874	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
22	13004	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
23	13443	1	1	1	1	1	1	1	1	1	1	1	3	3	2	2	1	2
24	13606	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
25	14371	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
26	14102	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
27	14909	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
28	15111	2	1	1	1	1	1	1	1	1	1	1	2	3	1	1	1	2
29	15547	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
30	15986	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
31	16100	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
32	16746	3	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
33	16547	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
34	17317	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2

S.NO	I.P. NO	AGE	PARITY	UTERINE ARTERY			UMBILICAL				MCA		DELIVERY	COND ON DELIVERY	MATURITY	APGAR 1MIN	APGAR 5 MIN	NNC
				PATTERN	HIGH RESI	E.D.N	PATTERN	HIGH RESI	AEDF	REDF	PATTERN	IDF						
35	17671	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
36	17498	2	1	1	1	1	1	1	1	1	1	1	1	3	2	3	2	3
37	18870	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
38	18470	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
39	19207	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
40	19530	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
41	19411	2	1	1	1	1	1	1	1	1	1	1	2	3	1	1	1	2
42	20107	2	1	1	1	1	1	1	1	1	1	1	1	3	2	1	1	2
43	20561	2	1	1	1	1	1	1	1	1	1	1	1	1	1	3	3	2
44	21199	1	1	1	1	1	1	1	1	1	1	1	3	3	2	1	1	2
45	21311	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
46	21576	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
47	22276	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
48	22494	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
49	23197	3	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
50	23301	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
51	23798	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
52	24674	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
53	24476	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
54	25196	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
55	25498	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
56	25863	1	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
57	26013	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
58	26987	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
59	27078	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
60	27490	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
61	27173	2	1	1	1	1	1	1	1	1	1	1	2	3	1	1	1	2
62	27986	2	1	1	1	1	1	1	1	1	1	1	3	3	2	1	1	2
63	28196	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
64	28765	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
65	29346	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
66	29769	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
67	29627	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
68	29981	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
69	30233	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
70	30601	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2

S.NO	I.P. NO	AGE	PARITY	UTERINE ARTERY			UMBILICAL				MCA		DELIVERY	COND ON DELIVERY	MATURITY	APGAR 1MIN	APGAR 5 MIN	NNC
				PATTERN	HIGH RESI	E.D.N	PATTERN	HIGH RESI	AEDF	REDF	PATTERN	IDF						
71	30176	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
72	30596	2	1	1	1	1	1	1	1	1	1	1	1	3	2	1	1	2
73	31078	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
74	31348	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
75	31127	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
76	31396	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
77	32274	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
78	31578	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
79	31899	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
80	32473	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
81	32078	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
82	33107	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
83	32814	1	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
84	33178	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
85	33489	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
86	34072	3	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
87	34192	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
88	34546	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
89	34303	2	1	1	1	1	1	1	1	1	1	1	3	3	2	2	2	2
90	33701	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
91	34671	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
92	35010	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
93	34371	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
94	34123	2	1	1	1	1	1	1	1	1	1	1	3	3	1	2	1	2
95	35517	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
96	35496	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
97	35312	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
98	36611	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2
99	36445	2	1	1	1	1	1	1	1	1	1	1	3	3	1	1	1	2
100	36938	2	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	2