IDENTIFICATION OF NOVEL BIOMARKERS FOR GESTATIONAL PREECLAMPSIA

A PROJECT SUBMITTED

TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy

BY

KHUSHALI. PARESHKUMAR. PATEL (16BPH041)

Semester VIII

UNDER THE GUIDANCE OF

DR. JIGNA SHAH

INSTITUTE OF PHARMACY
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SARKHEJ-GANDHINAGAR HIGHWAY
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GUJARAT, INDIA

APRIL 2020

CERTIFICATE

This is to certify that ***"Identification of Novel Biomarkers for Gestational Preeclampsia"*** *is the bonafide work carried out by* ***KHUSHALI PATEL*** *(16BPH041), B. Pharm semester VIII under our guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2019 to 2020. This work is up to my satisfaction.*

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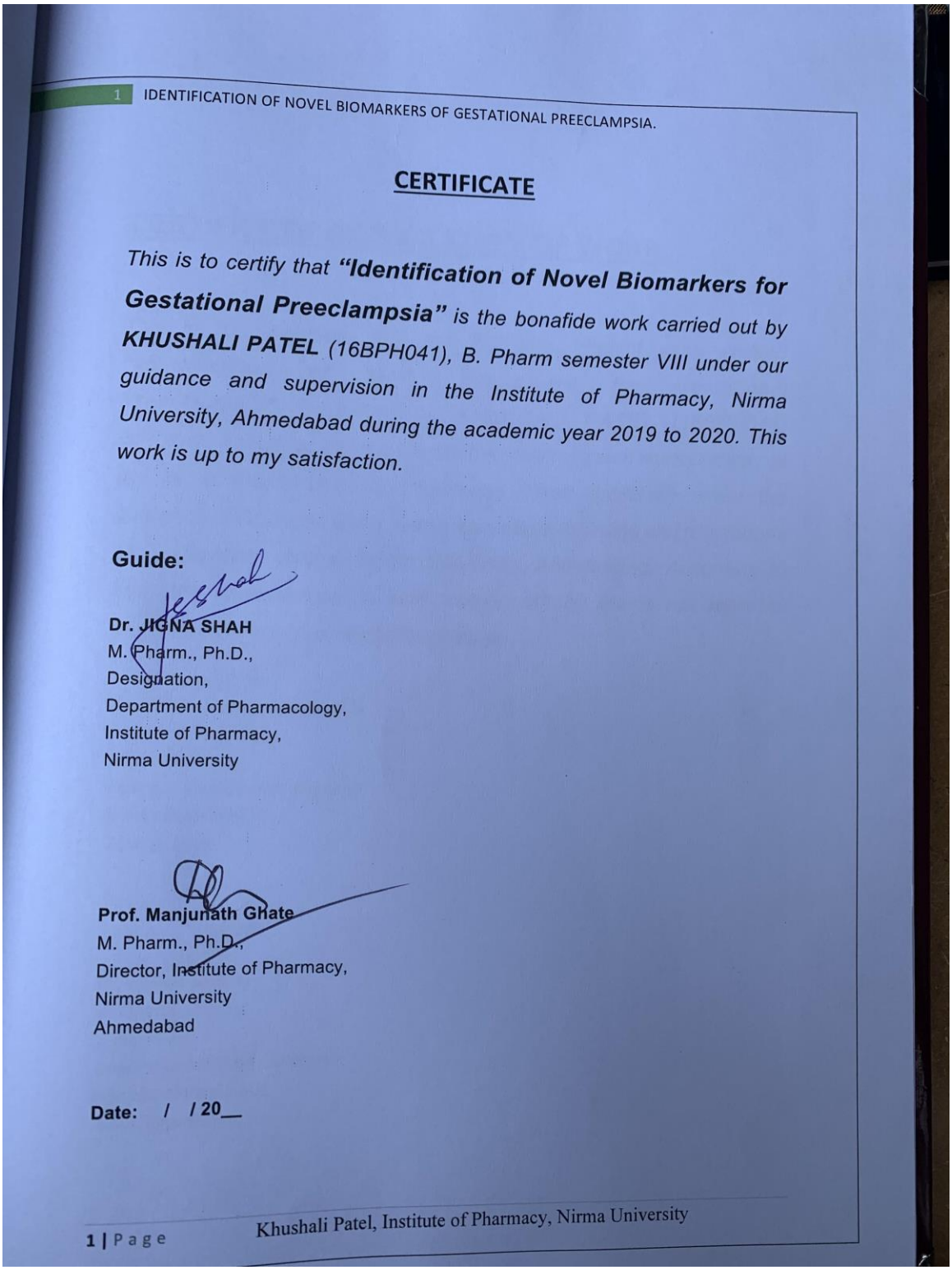

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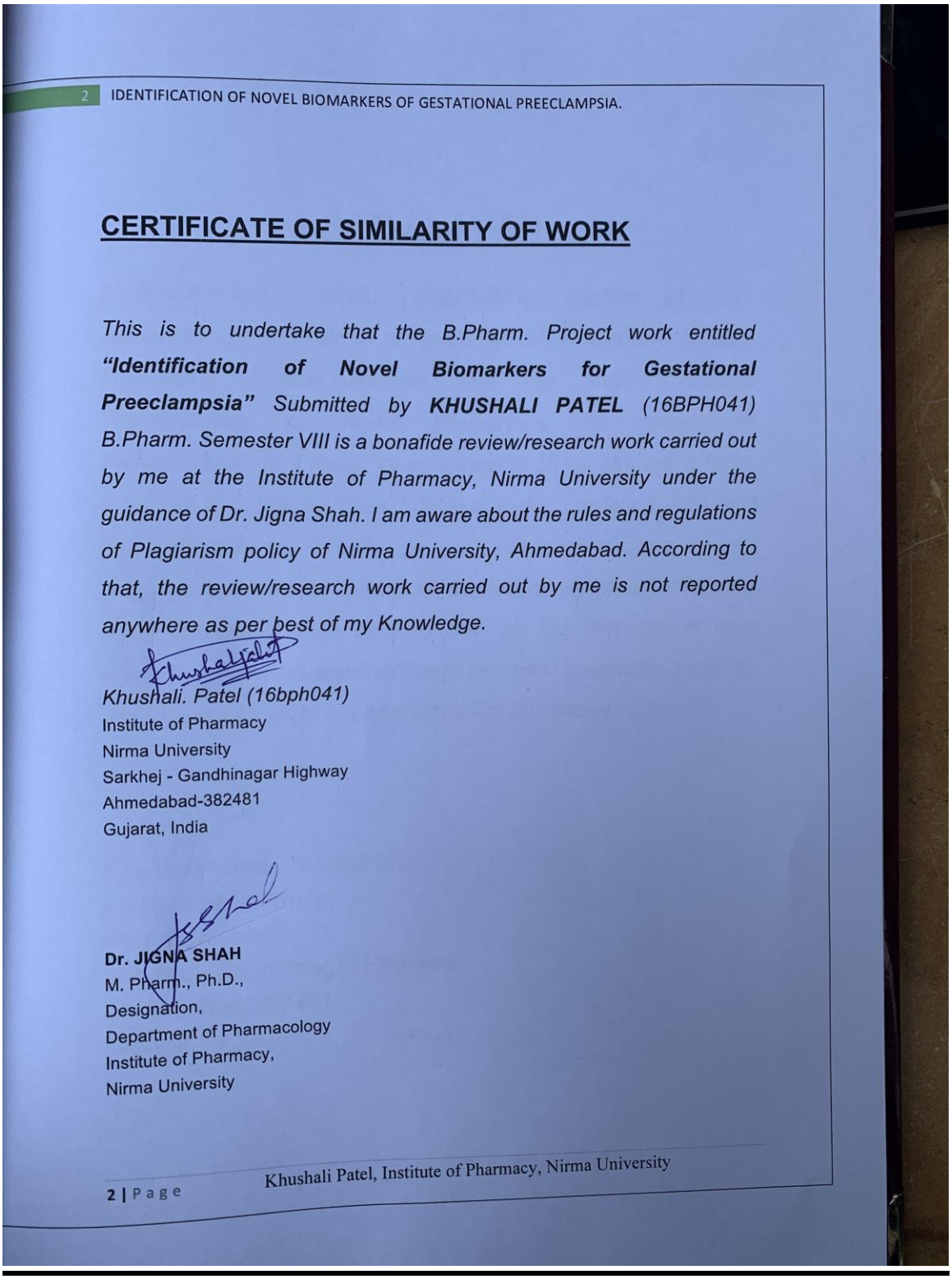

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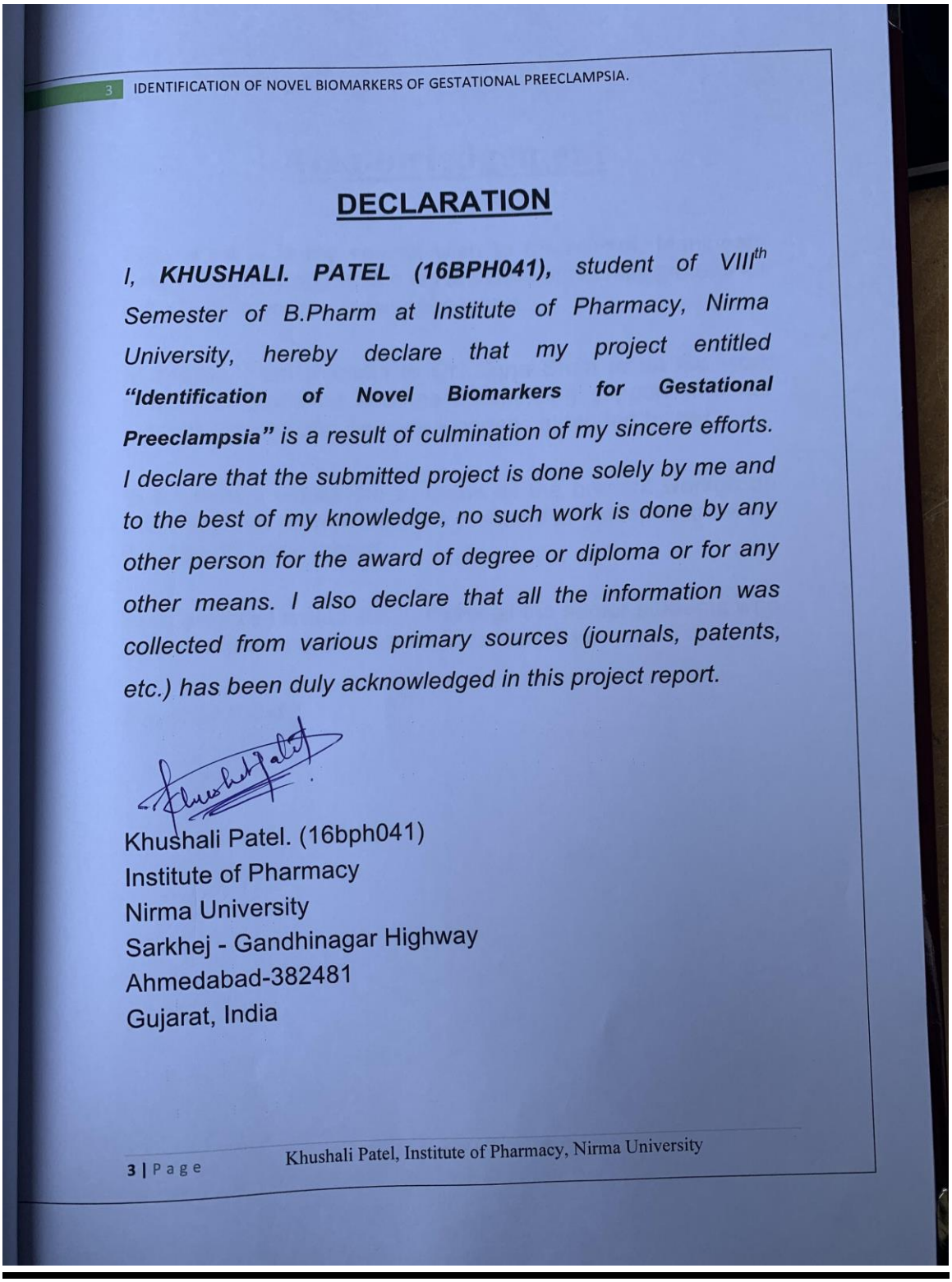

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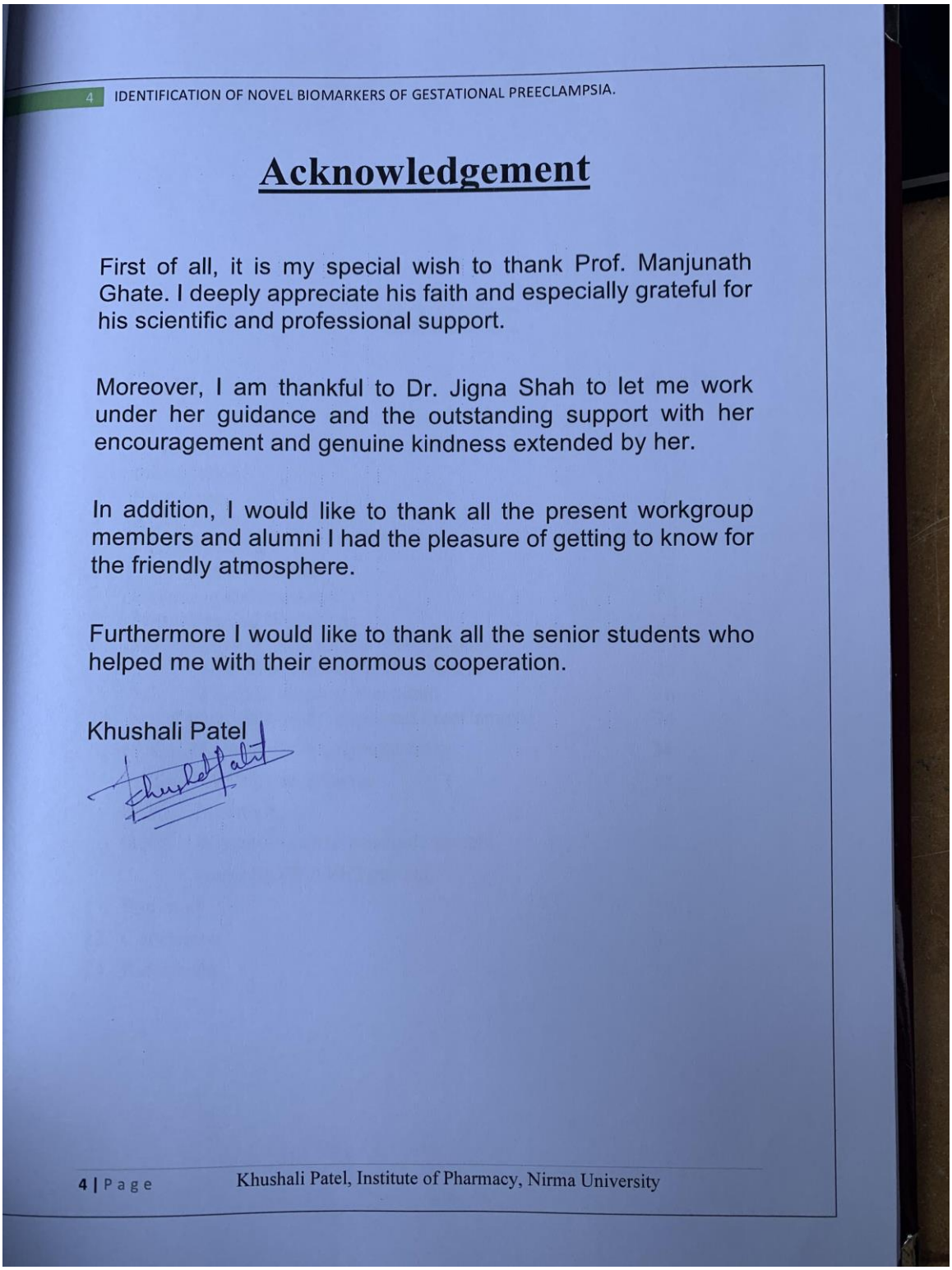

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CONTENT

i. List of Abbreviations

1. PE - Preeclampsia
2. BP - Hypertension
3. H/R - Hypoxia Reoxygenation
4. Mm hg - Millimeters of Mercury
5. HCG - Human Chorionic Gonadotropin
6. CVD - Cardiovascular Disease
7. UTI - Urinary Tract Infection
8. mg/Dl - Milligram per deciliter
9. hb - Hemoglobin
10. IUGR - Intrauterine Growth Restriction
11. P/C - Protein/ Creatinine Ratio

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1. ABSTRACT

Preeclampsia is a complex disease whose clinical evaluation varies with wide vaiety of unpredictable clinical manifestations and adverse effects with complicated health outcomes for mother and foetus during and post pregnancy. Though surprisingly, prevention and prediction of gestational preeclampsia with hypertensive abormalities has proven to be a core challenge for professional workers/physician. Multifarious strategies are developed to predict and diagnose the disease at early age of gestation to prevent unwanted complications during pregnancy and at the time of delivery. Still, most of the studies remains unconclusive constant attempt are going on through systematic research and reviews by conductuing surveys to understand detailed pathophysiology and pathogenesis of occurrence of preeclampsia and related complications during gestation. Since, no reliable tests results are proven to be succssful for predicting preeclampsia, heath care professionals gather their core interest in diagnosis of preeclampsia by relevent indications and risk factors with biomarkers. In this review, basic concept of gestational compliactions is discussed with considering preeclampsia during pregnancy. Detailed analysis on occureence of disease at early stage of development with it's pathophysiology is discussed. Elaborated knowledge on diagnostic and preventive mathods are discussed with various management therapies depending on the severity of the disease in a patient. Lastly, novel biomarkers to predict gestational preeclampsia is focussed upon to extrafoliate and modify exsisting strategies.

2. INTRODUCTION

Preeclampsia is said to be a remarkable cause of maternal morbidity and fetal mortality. It is a condition that occurs after week 20 of gestation period. Severe heart related complication and

metabolic dysfunction syndromes are observed in preeclamptic women and children at later stage of lifespan. Signs of liver and kidney damage with promptly high atrial hypertension (>140/90 mmHg) during gestation is noted whereas in rare case preeclamptic condition may develop in women after deliver within 48hours which is called postpartum preeclampsia.

Exact cause of gestational preeclampsia is still unrevealed though condition is thought to be placental origin. However, autoimmune disorders, genetics factors and diet habits may contribute to the severity of the disease. , geographical factor majorly plays a role in development of adolescent pregnancy. Various systematic reviews and surveys postulated that low income countries and medium income countries have larger prevalence of morbidity and mortality of gestational preeclampsia and eclampsia. Though being a fast-developing country, India lags behind in achieving maternal mortality rates of World Health Organization. Referral has been generated on the reliable literature for improvising diagnostic procedures and management therapies of preeclampsia to decline maternal mortality rates. Potentials of various biomarkers to predict preeclampsia are postulated recently whose exact mechanism of action is unrevealed that need to focused upon during clinical research studies. Moreover, preterm birth occurring prior to 37 weeks of gestation may lead to higher risk factors. The consequences of preterm delivery results in long or short term gastrointestinal or respiratory complications with neurodegenerative disease. Furthermore, preterm birth leads to various chronic diseases in adulthood like hypertension, diabetes, obesity etc. Higher weight gain is positively associated with the risk of development of gestational preeclampsia and eclampsia. Risk elevation was restricted to mild and moderate preeclampsia with unwanted deviation in diastolic

blood pressure. In accordance with previous findings, it was observed that an increased risk for pre-eclampsia was associated with null parity, high blood pressure, high maternal weight and with previous pre- eclampsia.

3. PREVALENCE

Various studies proclaimed that nulliparous women were more prone to preeclampsia development with adolescent pregnancy. Though they are less affected by co-morbidities such as hypertension, gestational diabetes mellitus etc. Adolescent pregnancy is prevalent not only

by individual biological status but can get largely affected by social, economical and educational structures of an area where an adolescent live. Many findings supported hypothesis that lack of education and social inequality may increase the rate of cases of adolescent pregnancy which further elevates the rate of gestational complications including preeclampsia and hypertension. Henceforth, geographical factor majorly plays a role in development of adolescent pregnancy. Various systematic reviews and surveys postulated that low income countries and medium income countries have larger prevalence of morbidity and mortality of gestational preeclampsia and eclampsia by 11.6% and 9.3% respectively than well developed areas of the world. Further findings may limelight financial welfare which undoubtedly remains core factor for prevalence and cure of pregnancy with preeclampsia and eclampsia. Insufficient calcium intake during early pregnancy can lead to gestational hypertension which if not considered can result in fetal complications. Recently conducted meta-analysis in 76 studies within 26,762 women in Asian countries gave an idea of adding calcium supplements at early stage management of pregnancy to prevent occurrence of preeclampsia and eclampsia than just rendering upon micronutrients supplements.

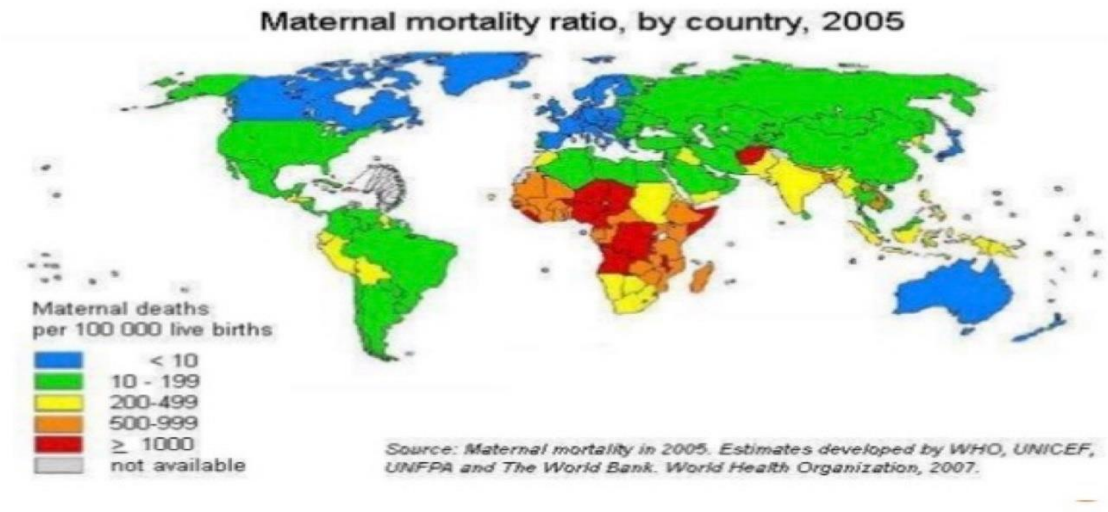

Figure: 1 Maternal Mortality throughout the world

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at early stage management of pregnancy to prevent occurrence of preeclampsia and eclampsia than just rendering upon micronutrients supplements.

Around 1980, the proportion of adolescent pregnancy rate elevated which is now declining in majority of countries, whereas surprisingly trend has expected to continue till 2050. However, number of adolescents will increase during the same period of time. As per United Nations International Children Emergency Fund's data of 2017, teenagers make 21% of population and more than half majorly lives in Asia (53% of South Asia homes with 342 million of adolescents and East Asia and Pacific region comprising of 211 million of teenagers, whereas 32.4% in Africa and 8.3% in Latin Europe. Lastly, 5.3% in central and western Africa and Commonwealth of Independent states (CEE/CIS).

(European Journal of Obstetrics and Gynecology and Reproductive biology, Volume 248 May 2019, pg;192-194.)

4. RISK FACTORS AND COMPLICATONS

4.1 Complications

Complications include fetal death or fetal growth impairment. Multifocal vasospasm may end up in maternal ischemia, eventually damaging major functioning organs like brain, liver and kidney. Decreased prostacyclin (vasodilator) and increased endothelin, elevated soluble Flt-1 profoundly contribute to vasospasm. Women with preeclampsia is suspectable of abruption placenta in current or in future pregnancies.

Furthermore, activation of coagulation system takes place, which results in endothelial dysfunction and inversely causes platelet activation. Majority of women faces HELLP syndrome (hemolysis, elevated liver function which leads to immediate platelet activation) have elevated blood pressure and proteinuria, but some have neither.

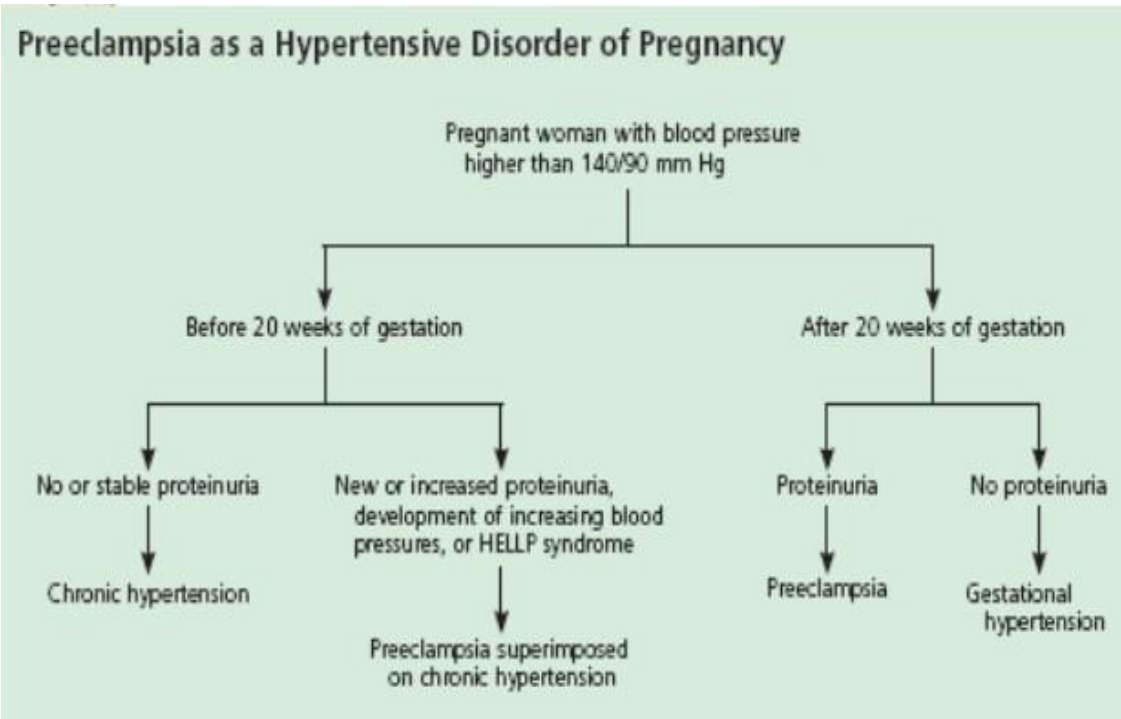

Figure: 2 Development of Hypertensive Disorder

An algorithm of differentiating hypertension disorder in pregnant women can be illustrated from above mentioned chart. Further complication leads to peripheral edema due to accumulation of fluids in joints or organs of the pregnant women during 16 to 20 weeks of gestation.

4.2 Risk factor for Gestational Preeclampsia

- Urinary tract infection
- Structural congenital anomality
- Chromosomal abnormalities
- Hydatidiform mole
- Hydrops fetalis
- Maternal specific factors
- Age more than 35 years
- Multifetal pregnancy
- Nulliparity
- Family history of preeclampsia

- Age less than 20 years
- Specific medical conditions like thrombophilia
- Diabetes type 1 history

Risk factors are taken to consideration with involvement of diagnostic procedures and then after management can be assessed with pharmacological and non-pharmacological parameters to prevent severity of the worsened condition during gestation.

5. PATHOPHYSIOLOGY OF PREECLAMPSIA

Pathophysiology of preeclampsia can be elaborated with the help of maternal factors and fetal factors with results in abnormal placental vasculature followed by placental ischemia. Moreover studies reflected presence of vasoactive substances like cytokines, radicles and peroxides in the system which escalates fatality of the condition that ends up with endothelial damage. Thromboxane prostacyclin disparity leads to progress in glomerular leak, activation of coagulation and aggregation which results in proteinuria and diffuse intranasal coagulation. Furthermore, uterine renin angiotensin-aldosterone causes sodium and fluid retention that leads to capillary leak contributing to edema whereas vasoconstriction elevates blood pressure of the body resulting in hypertension.

Lipid peroxidation radicals present in cell membrane may contribute to the progression of gestational preeclampsia. The initial events in pathogenesis of preeclampsia includes placental ischemia which alternatively elaborate variety of biological events that grows profound effects on cardiovascular system. Several factors are lime lighted such as soluble forms of angiotensin 2 type 1 receptor antibody, soluble tyrosine kinase-1, and cytokines like tumor necrosis factor alpha which unknowingly effects maternal vascular endothelium.

(Adiponectin and insulin resistance in early- and late-onset pre-eclampsia. Br J Obstetrics Gynecology. 2006;113:1264–1269.)

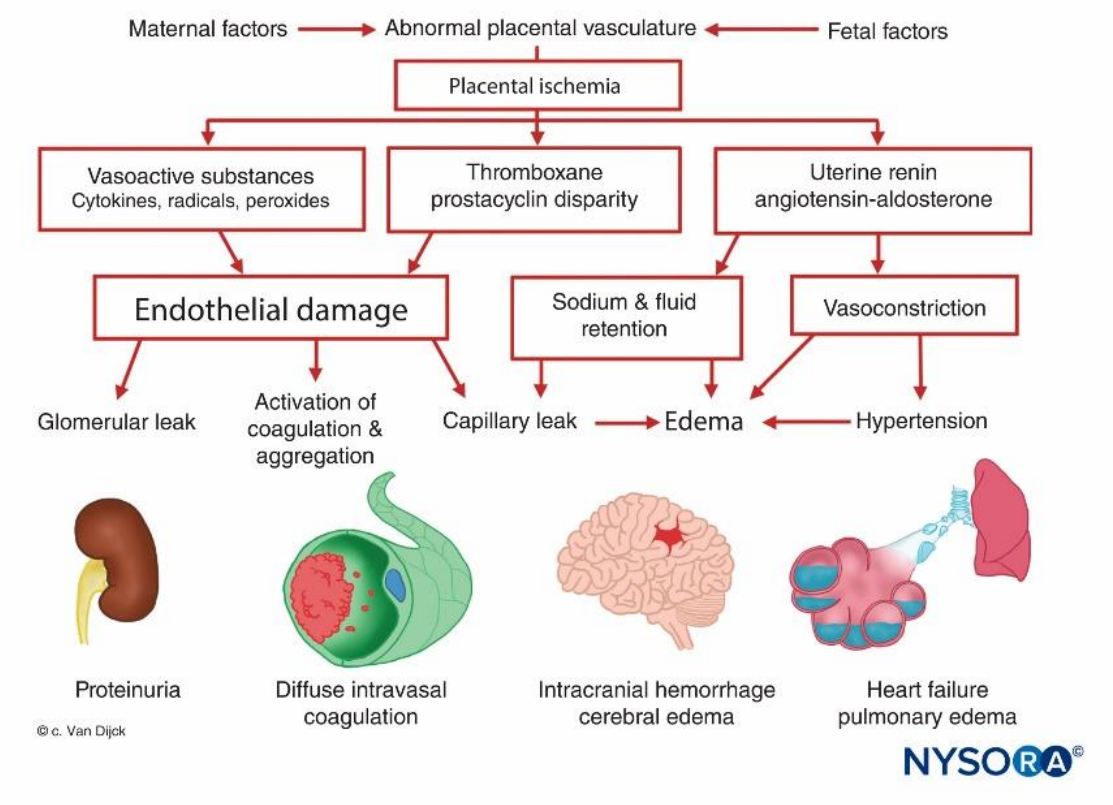

Figure: 3 Pathophysiology of occurrence of Preeclampsia

Predisposition of hypertension and diabetes leads to failure in conversion of spiral arteries to vascular sinuses which provokes gestational ischemia due to placental production of thromboplastins leading to growth retardation of fetus if preeclamptic condition continues uninterrupted or untreated, eclamptic stage may occur.

Several studies found that hormonal factors may contribute to early stage of preeclampsia. It is associated with very low estrogen and progestrogen level and elevated Human Chorionic Gonadotrophin (HCG) level. Occurrence of abnormal sex ratios at birth are noted due to hormonal imbalance during gestation period of a woman. Multifarious studies have propagated the relation between gestational induced hypertensive disorders with gender, though results were found to be contradictory. Lipid peroxidation radicals present in cell membrane may contribute to the progression of gestational preeclampsia. The initial events in pathogenesis of preeclampsia includes placental ischemia which alternatively elaborate variety of biological events that grows profound effects on cardiovascular system. Several factors are lime lighted such as soluble forms of

angiotensin 2 type 1 receptor antibody, soluble tyrosine kinase-1, and cytokines like tumor necrosis factor alpha which unknowingly effects maternal vascular endothelium. Due to abnormal unwanted activities, there is profound formation of factors such as endothelin, augmented vascular sensitivity to angiotensin-2, radicles or reactive oxygen species. Alternatively, generation of preeclamptic symptoms may induce formation of vasodilators like nitric oxide and prostacyclin. These results in renal pressure elevation which increases peripheral resistance and contributing positively to gestational hypertension. Moreover, multifarious humoral factors and endothelial factors mediate vasoconstriction and occurrence of arterial pressure during gestational preeclampsia remains to be elucidated.

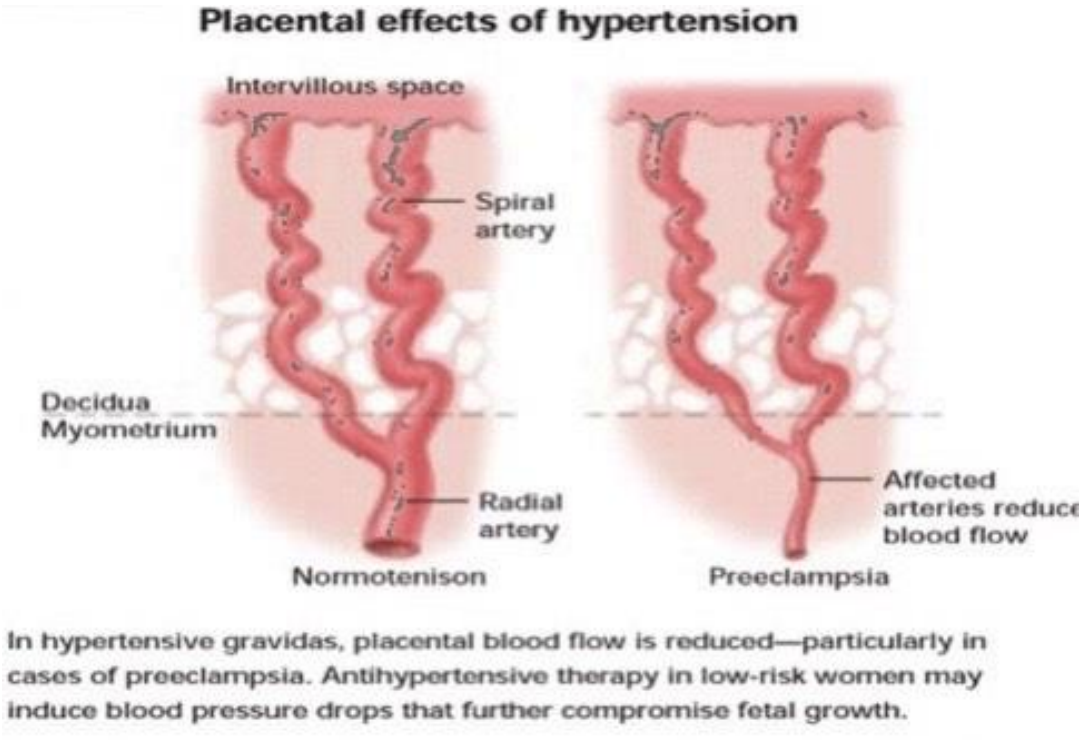

Figure: 4 placental effect of hypertension

Pathophysiology includes malfunction of poorly developed placental uterine spiral arterioles, which decreases utero placental blood flow pressure during last stage of pregnancy. Further genetically linked abnormality in chromosome 13, placental ischemia, abnormalities related to

immunology or infraction. Lipid peroxidation radicals present in cell membrane may contribute to the progression of gestational preeclampsia

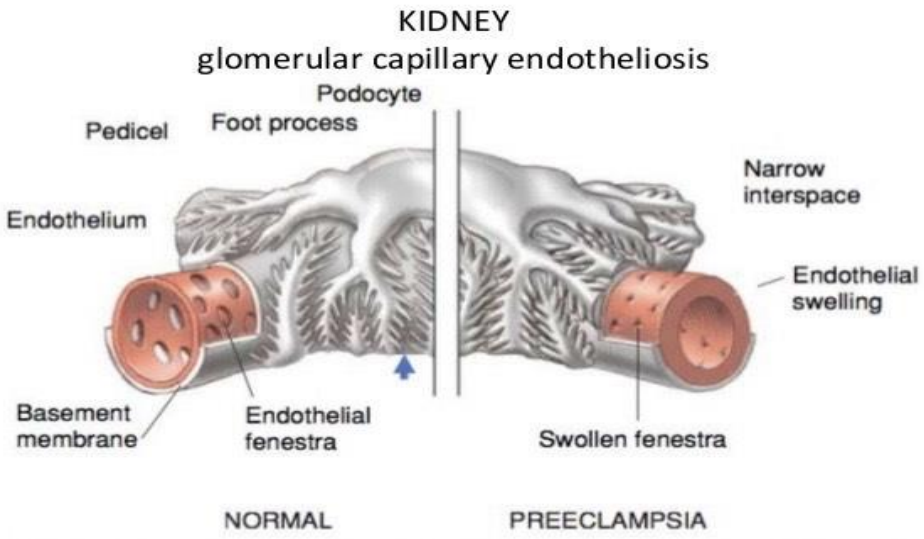

Figure: 5 Schematic diagram showing glomerular capillary endotheliosis

The capillary of the normal glomerulus is shown with broad endothelial fenestration, and the pedicels emerging from podocytes are widely spaced, whereas the illustration of glomerulus with swollen fenestra induced by the preeclamptic condition. The endothelial cells are slightly swollen and their fenestrate is narrowed, which results in altered functioning in pedicels.

6. CLINICAL MANIFESTATION

Early stage occurrence can be manifested by observing various symptoms and signs which helps in diagnostics evaluation of preeclampsia. Preeclampsia sometimes develops without any symptoms. Hypertension may invade slowly or can also lead with sudden onset. Management and monitoring of blood pressure is a vital part of prenatal care as it is the first sign of initiation of preeclampsia. Diastolic blood pressure exceeding 140/90 mm hg or greater is documented on two occasions which is considered abnormal.

Other signs and symptoms of gestational preeclampsia comprise of:

- Severe headaches
- Changes in visions which includes temporary loss of vision or blurry eyes
- Excessive protein in urine (proteinuria) or renal dysfunction
- Nausea and vomiting
- Thrombocytopenia (decreased level of platelets)
- Retention of fluid in lungs causing shortness of breath.
- Impaired liver function and low first pass metabolism
- Abdominal pain usually under ribs on the right side.

Rapid weight gain and swelling of hands, legs and face may occur with preeclampsia. However, swelling may occur in normal pregnancy hence it is not considered as a sign or symptoms for the initial occurrence of gestational preeclampsia.

7. DIAGNOSIS

Several tests are performed to diagnose gestational preeclampsia during 20-25 weeks of pregnancy. There are blood tests that include kidney function tests, liver function tests and also diagnose platelet counts known as blood clotting factor. Urine analysis can be performed by the measurement of urine sample of an individual collected before 24 hours, the ratio of protein to creatinine is taken into consideration. Closed examination of growth of baby can be done through fetal ultrasound. After ultrasound examination, obtained images gives presential idea of fetal weight and fluid retention in uterus also known as amniotic fluid. Furthermore, nonstress test or biophysical profile is carried out to diagnose fetal heart rate during casual movements within the uterus. Volume of amniotic fluid, fetal muscle tone, fetal breathing can be examined by biophysical profiling... The International Society for Study of Hypertension in Pregnancy (ISSHP) declared usage of urinary protein/creatinine ratio as an alternative method in early stage diagnosis of gestational fluid retention. Ubiquity of microalbuminuria is detected marker of systemic endothelial cell dysfunction and is noted to be a hallmark component of diabetic nephropathy.

7.1 Diagnostic Evaluation

Pregnant women should be interrogated about their obstetric history, their medical history including preeclampsia, collagen vascular disease, diabetes mellitus, urinary disease, hypertension and phospholipid antibody complication.

During prior evaluation after 18 weeks of pregnancy, women were asked interrogated their current symptoms of vision, and epigastric pain. Questions should be framed in standardized documentation of prenatal forms.

7.1.1 Physical Examination

Previously studies baseline (>30mm Hg systolic or 15mm Hg diastolic) are no longer accepted in current studies. To manifest exact readings, relevant hypertension cuff should be taken, and hypertensive stage should be evaluated only after a buffer period of 10 to 15 minutes of brisk walking. Left lateral recumbent position of patient should be checked with hands at the level of heart.

Foetus development must be evaluated at every visit to avoid intrauterine growth retardation or oligohydramnios. Keen observation on rapid weight gain and maternal facial edema should be checked upon regularly to avoid unwanted fetal fluid retention the body of patient.

7.1.2 Laboratory Evaluation and diagnosis

The level of uric acid in serum was previously used as a biomarker for gestational preeclampsia and eclampsia but then after it was found to proclaim that it acquires least specificity as a diagnostic parameter. However, increased level of uric acid can be still evaluated as chronic hypertension in pregnancy with superimposed preeclampsia. Multifarious tests should be performed in early stage of gestation to avoid unavoidable severe conditions.

A baseline laboratory tests include;

- Hepatic enzyme level
- Platelet count
- Serum creatinine level

- Protein measurement

Several laboratory tests with their normal ranges are listed below in the table. Elevation or decline in levels of parameters may be an alarming hint for occurrence of gestational preeclampsia in certain pregnant women.

Table: 1 Laboratory tests with their normal range

Hemoglobin level	12 to 15.5 grams per deciliter.
Platelet count	1,50,000 to 450,000 per microliter of blood
Urine protein collection (12 or 24 hour)	Less than 250mg is considered normal
Serum creatinine level	0.5 to 1.0 mg/dL
Serum uric acid level	2.4 to 6.0 mg/dL
Serum transaminase level	10 to 40 units per liter
Serum albumin level	3.4 to 5.4 g/dL
Lactic acid dehydrogenase level	140 to 280 U/L
Serum transferrin level	170 370mg/dL

7.2 Indications of preeclampsia

Indications of severe preeclampsia for urgent delivery now regardless of gestational age;

- Pregnancy more than 34 weeks
- Severe hypertension (more than 160/110 mm hg)
- Fetal complication
- Placental Abruption
- Hands and legs swelling (edema) and eclampsia

Indications of delivery within 48 hours of taking Corticosteroids during 23-30 weeks of pregnancy with severe preeclampsia;

- Non-reassuring fetal testing
- Severe oligohydramnios
- Increase in serum transaminase levels (almost double)
- Retardation of intra uterine growth. (IUGR<5 %)
- Reversion of Umbilical artery hence disrupted end diastolic flow.
- Degrading renal efficiency

Indication of cesarean delivery or vaginal delivery (more preferred)

- Severe Preeclampsia with abnormal cervix at less than 30 weeks of gestation
- Refractory, severe hypertension (>160/110 mm hg)
- Recurrent Seizures due to drug interactions
- Fetal or maternal abnormalities without delivery.

Precautions

- Avoid epidural or spinal anesthetic if platelet count is less than <70k,
- Coagulopathy should be performed priorly.
- Antiplatelet therapy.

World Health Organization systematic review of management of dose for preeclampsia. Obstet Gynecol. 2004;104:1367–1391.

8. MITIGATION AND PREVENTION

Complicated development of preeclampsia may occur in case of multifetal gestation.Preeclampsia develops with respect to restricted fetal growth of one of the fetus resulting in dyfunction of prematured organs.

Several methods were taken into consideration to retard degenerative effect of preeclampsia on developing baby. One of the twin was linked to lethal condition of preeclampsia and was treated with selective feticide to reverse the effect of preeclampsia.

Antiplatelet therapy can be accessed before or after 15 weeks of gestation with low dose of aspirin to prevent morbility and fetality caused by preeclamptic stage on the foetus.Consumption of food bars containing L-arginine and antioxidant vitamins may prevent occurrence of preeclampsia during pregnancy.Doctor may induce labor in case of emergency which leads to early delivery to mitigate deletorious effect of the disease.Keeping healthy diet with controlling elevated blood pressure during gestation surely helps to reduce the risk of the preeclamptic condition.

Moreover, consumption of food bars containing L-arginine and antioxidant vitamins may prevent occurrence of preeclampsia during pregnancy.Doctor may induce labor in case of emergency which leads to early delivery to mitigate deletorious effect of the disease.Keeping healthy diet with controlling elevated blood pressure during gestation surely helps to reduce the risk of the preeclamptic condition.

About 3-5% of pregnant women are extremely affected by gestational preeclampsia. To minimize the adverse effects, preventive measures are taken into consideration based on alteration in lifestyle, nutritional supplements, and drugs therapy (nitric oxide, diuretics, progesterone, aspirin and calcium supplements) are recommended.

8.1 Prediction of Preeclampsia

An ideal way to predict preeclampsia includes appropriate biological and non-biological predictors. Due to immature placentation and pre-existing maternal disorders including poor vascular flow and increased BP. Hence, with respect to this assumption, studies rely upon occurrence of maternal poor vasculature with in early stage of gestation with and maternal history involving hypertension, uterine flow doppler, inhibin A serum markers as biomarkers.

Prophylactic interventions for mild gestations have not proven effective though reliable antenatal identifications are efficacious for clinical resources monitoring and usage of possible preventive and cost-effective treatment.

8.2 Importance of Prevention

Several factors have proven to complicate the preventive measures and increase maternal morbidities and mortality rates. Currently no prophylactic intervention has been advised to reduce the effect. Nowadays, treatment involves removal of placenta or delivery. But prophylaxis with moderate or small dose interventions are advisable for worthwhile. Several findings are dependent on primary interventions, when applicable to entire masses of people which includes;

- Bed rest
- Restriction regular workout
- Nutritional supplements
- Antioxidants (vitamin C, E)
- Antiplatelet therapy

Studies which are applied to high population includes;

Preventative therapy

Various study postulated that to prevent the severity of disease, various preventive therapies are designed with lists of medicaments used in the treatment to reduce adverse effects of preeclampsia and eclampsia on the fetus and mother. Calcium supplements are taken well in advance to avoid initial complications whereas antiplatelet therapy is suggested if extremely low platelet counts are observed during laboratory tests.

Table: 2 Preventive Therapy

Loop diuretics in combination with K sparing diuretics
Progesterone in combination with estrogens
Sodium Nitroprusside and S-nitro thiols
Calcium supplements like calcium gluconate
Aspirin as a blood thinning agent

8.3 Treatment Strategy

Table:3 Treatment goals for Preeclampsia

Mild Preeclampsia	**Severe Preeclampsia**	**Seizures**	**Follow ups**
Expectant	Admission	A, B, C	Reassess
Admission	Mgso4 4.2 g/hr	Oxygen stat	Discharge when stable
Betamethasone	Intrapartum(24hr)	Mgso4 4.2 g/hr	Mgso4 1day postpartum
MgSo4 4.2 g/hr	Postpartum(24hr)	MgSo4 2g bolus	Mgso4 1day post seizure
RCOG 1g/hr	IV Labetelol	Left lateral position	PO Methydopa
	Hydrazine	Prepare for delivery	PO Labetelol
	Nifedipine		Low dose Aspirin
	Decide on delivery		Monitor HELLP (corticosteroids)

9. MANAGEMENT OF PREECLAMPSIA

9.1 Non-Pharmacological Management

Safety of mother and delivery of a mature newborn who will require prolonged neonatal care should be the main management objective. This can be taken into consideration by formulating management plan that reflects rough idea about severity of disease, maternal and fetal status at prior evaluation level.

Antepartum management of mild hypertension and preeclampsia

Treatment before 37 weeks of gestation is considered controversial. Several parameters have been emphasized upon for optimum care of the women during mild or moderate conditions.

9.1.1 Bed Rest

Partial or complete bed rest is recommended during mild hypertension and mild preeclampsia for pregnant women but there is no randomized trials performed or recorded for the benefits lying underneath. Several studies depicted that entire bed rest during pregnancy can led to elevation in risk of thromboembolism.

9.1.2 Blood Pressure medicaments

Mild inclination of blood pressure during pregnancy is considered normal. Hence to avoid blood pressure medications or accepting placebo left out to be the best options to prevent unwanted effects of pregnancy by medicaments.

9.1.3 Maternal and fetal Surveillance

Several authorities recommended daily fetal movement count by considering biophysical profile and non-stress test. Several studies stated that there was reduction in uteroplacental blood flow during pregnancy so ultrasound estimation of amniotic fluid and fetal weight is managed at the time of diagnosis in a serial way after 3 to 4 weeks.

9.2 Management of mild preeclampsia and hypertension

During 37 weeks of gestation or more, if non-reassuring fetal status is observed or membrane rupture at 34 weeks or more then immediate delivery is suggested to prevent deleterious effects. In some cases, intrauterine growth restriction is observed. If above mentioned conditions do not occur then inpatient or outpatient management is done with maternal and fetal evaluation with balancing the level of prostaglandins.

Carbohydrate and lipid metabolism in pregnancy: Normal compared with gestational diabetes mellitus.. 2000;71:1256S–1261S.

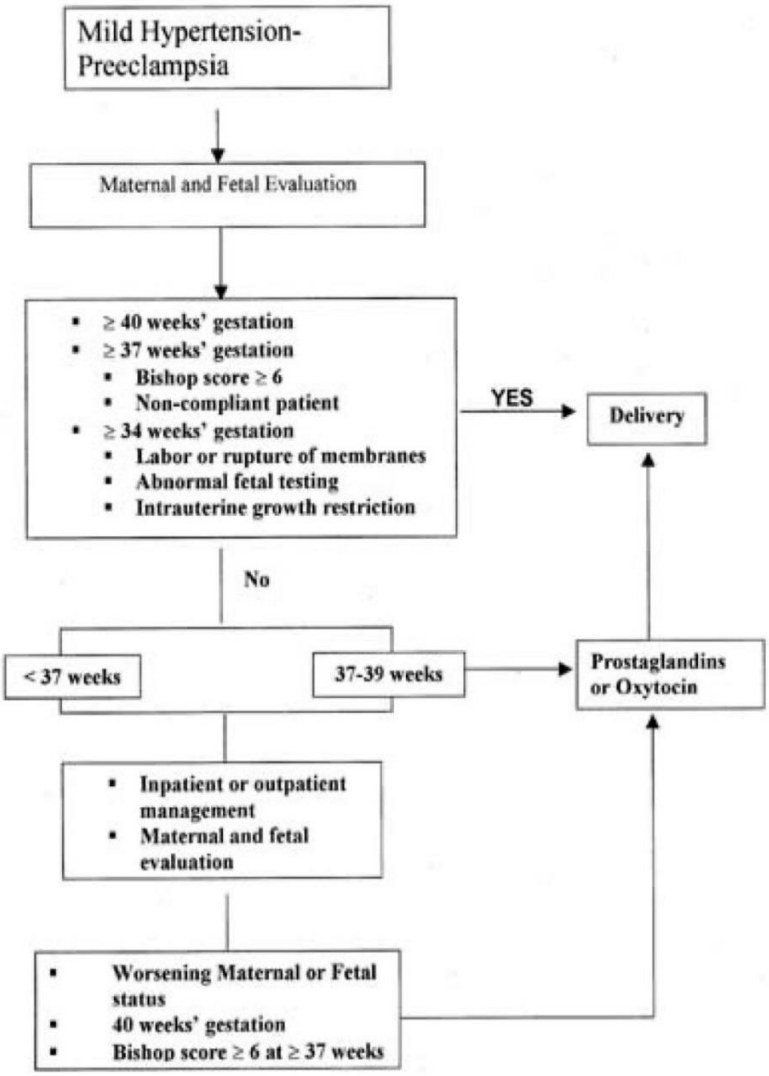

Figure: 6 Management of Mild Preeclampsia

9.2.1 Management of mild preeclampsia in secondary level

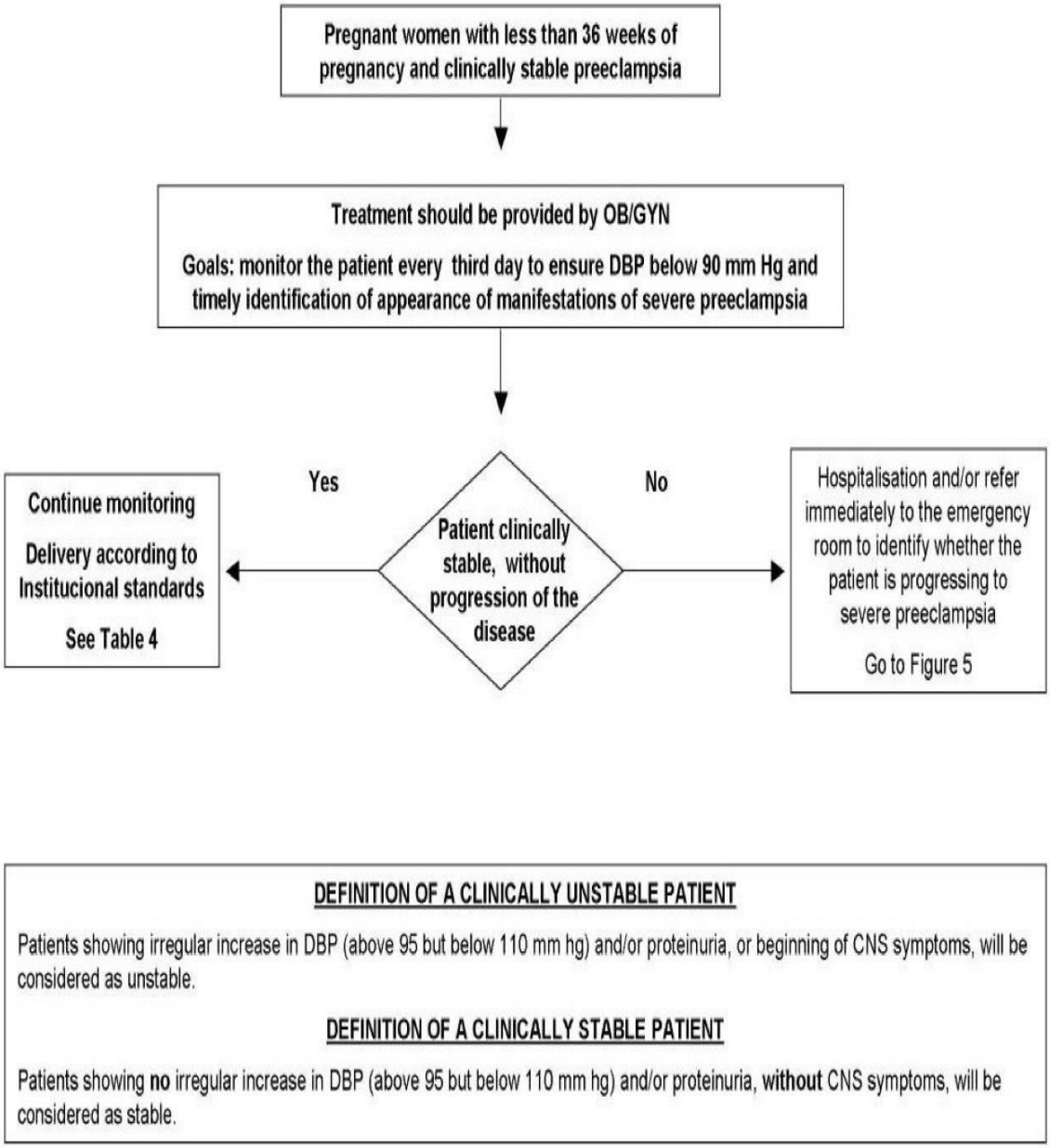

Figure: 7 Flowchart of management of mild preeclampsia in secondary level

Patient progress is elaborated by flowcharts by providing optimal timing and sequence order of staff actions. Hence, it proves to be a method of standardization of treatment and diagnose of disease along with physician responding individual patient's progression or complication.

9.3 Management of severe hypertension and preeclampsia

Uncontrolled conditions can be managed by immediate hospitalization or instant delivery. Several studies suggested to give magnesium sulphate intravenous to reduce risk of preeclampsia whereas mild antihypertensives to normalize the conditions. An ideal range of antihypertensive therapy states that to keep systolic blood pressure between 140 and 155 mm Hg whereas diastolic blood pressure between 90 and 105 mm Hg.

Addition of corticosteroids like prednisone or prednisolone is recommended during 27 to 32 weeks of gestation to increase the fetal lungs maturation. Maternal management of the epigastric pain, cerebral status, urine output and vaginal bleeding has to be evaluated.

Meanwhile, fetal evaluation of heart monitoring, and ultra-sonographic evaluation of fetal development and constant check on amniotic fluid is done. Patients with uncontrolled blood pressure after giving 225mg labetalol or 50mg nifedipine whereas persistent cerebral symptoms after giving magnesium sulphate, immediate delivery is suggested within 72 hours regardless of the gestational age.

Magnesium sulphate is a drug of choice to prevent convulsions during gestational preeclampsia instead of placebo treatment as mentioned as an outcome of randomized trials of about 1108 pregnant women. Currently no prophylactic intervention has been advised to reduce the effect. Nowadays, treatment involves removal of placenta or delivery. But prophylaxis with moderate or small dose interventions are advisable for worthwhile. Meanwhile, fetal evaluation of heart monitoring, and ultrasonic assessment of fetal growth and evaluation of amniotic fluid is done. Admit to labor and delivery area where constant maternal and fetal evaluation done 24 hours. Magnesium sulfate is administered.

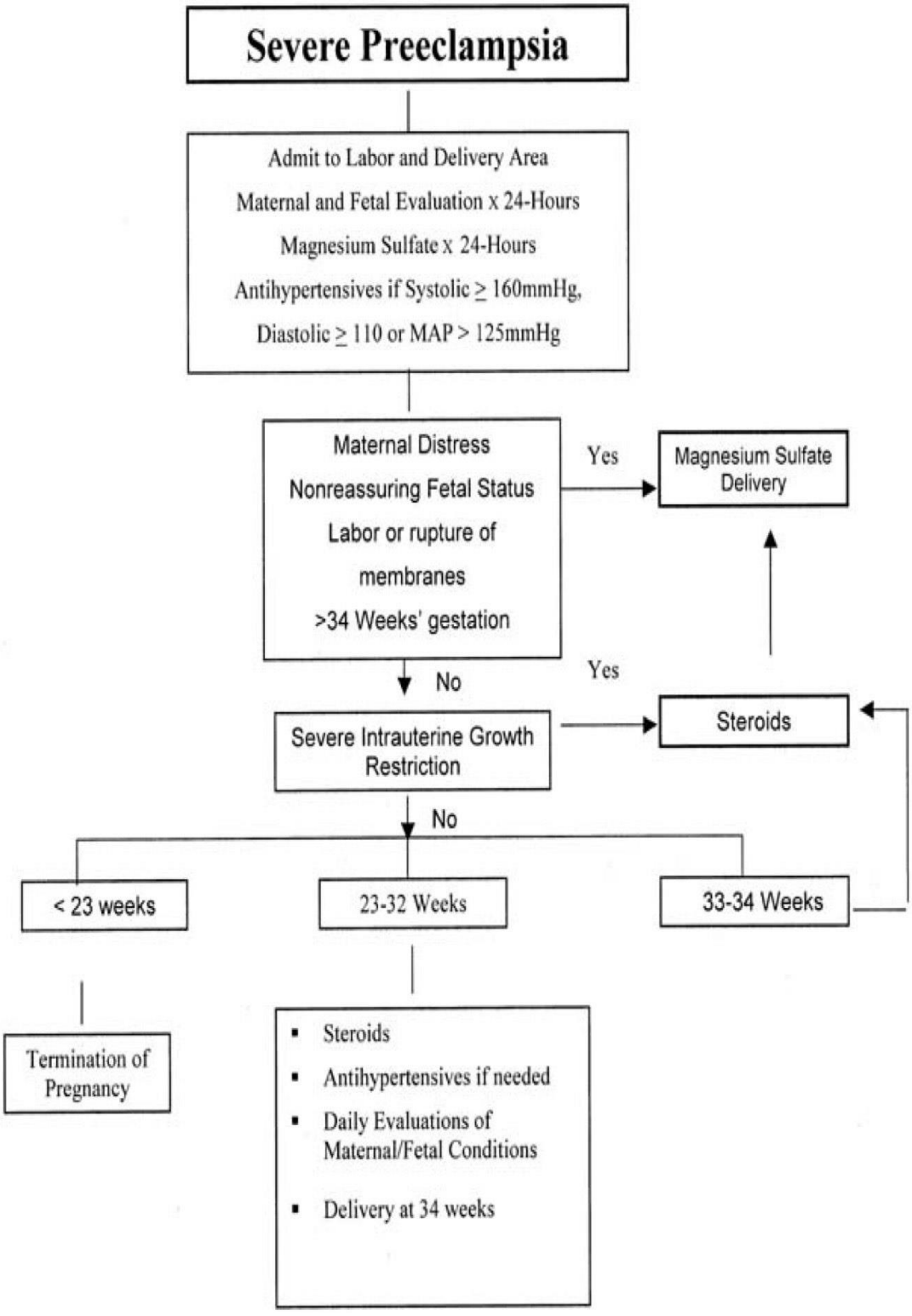

Figure: 8 Management of Severe Preeclampsia

9.4 Management of Clinically unstable Preeclampsia

The framework for the Critical Preeclampsia is based on the methodology proposed by the Care Resource Group and it was evaluated and taken into consideration accordingly. Relevant method to follow in clinically unstable preeclampsia are elaborated using flowcharts... The pathways present a method which defines interventions should be performed according to the health status and evaluated by level of care and medicine provided.

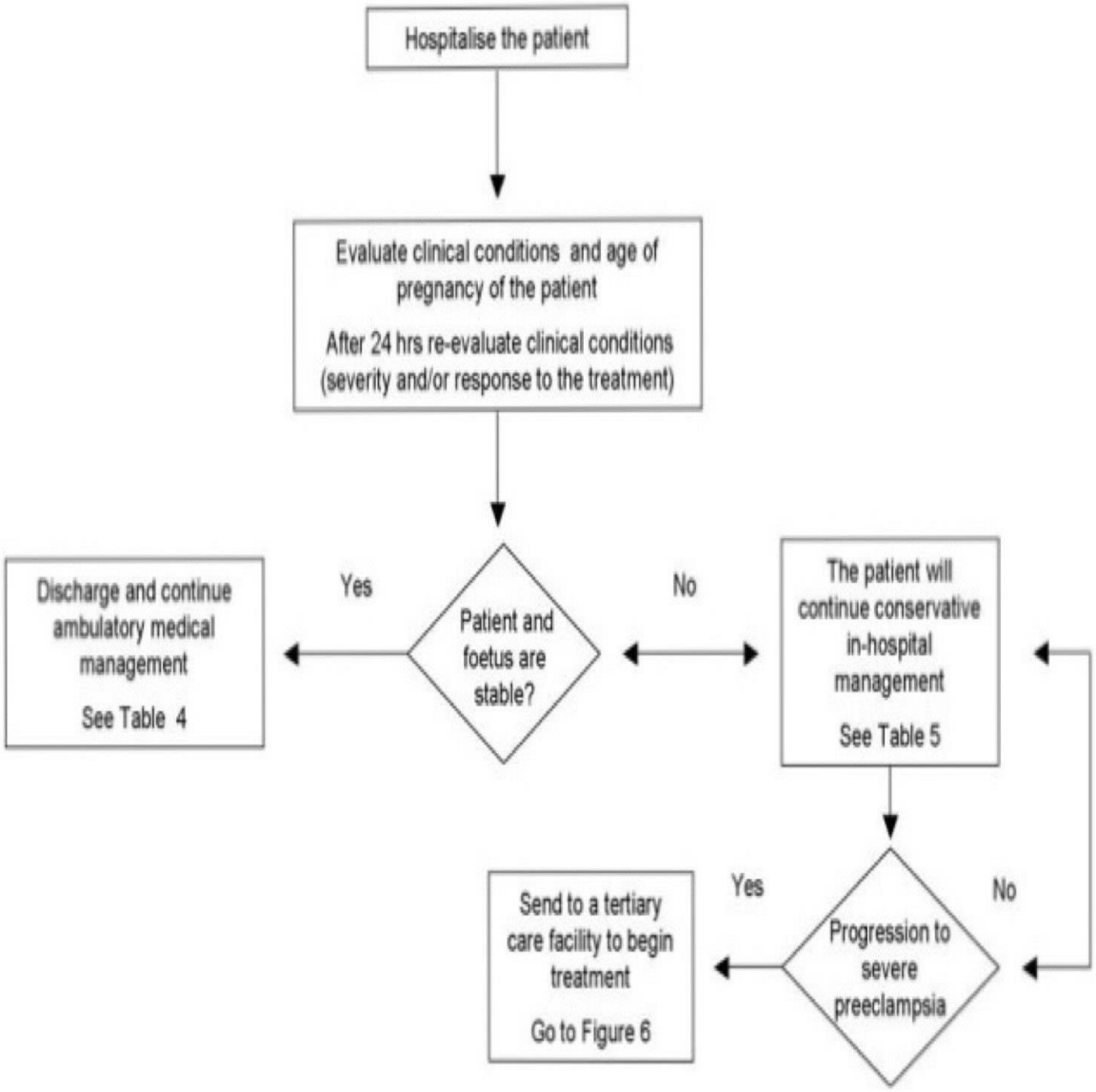

Figure: 9 Management of clinically unstable Preeclampsia

The analysis was restricted to 85% of data for particular outcomes. Randomized trials were performed on the women with the intension to treat. The level of heterogenicity was assessed with I square statistics and the mixed effect model was taken into consideration.

There was no statistical difference between the outcomes of two subgroups of women with gestation before and after 16 weeks of gestational age (P=0.98, Heterogenicity=25%) for the 4 main outcomes. Result did not show any relevant difference between subgroups of randomized women to antiplatelet therapy before and after 16 weeks of pregnancy.

9.5 Pharmacological Management

Magnesium sulfate: Continuous infusion of 2gm Loading dose 4-6 g diluted in 100ml normal saline over 15-20 minutes.

Labetalol: 20mg IV * 1 dose; if patient does not respond positively slightly elevate dose to 40 milligrams and then after 10 minutes of interval increase the dose to 80 milligrams until targeted blood pressure is accomplished (maximum range of dose 220milligram).

Hydralazine: Initial dosage is repeated as needed when hypertension is controlled (range maximum up to 400 milligram each day). If in case blood pressure is out of control from the normal range then reconsider the initial dose and evaluate every 20 minutes. Uncontrollable conditions are improved by considering different option of anti-hypertensive drugs. For example, Nifedipine and Sodium Nitroprusside. 5-12 milligram intravenous every 15 to 20 minutes (avoid using maximum dosage of 25milligram of drug).

Betamethasone: 12mg intramuscular * 1 dosage, then after repeat the dose each day.

Dexamethasone: 6 milligram * 1 dosages, then after repeat the dose every 12 hours with subsequent 3 extra dose.

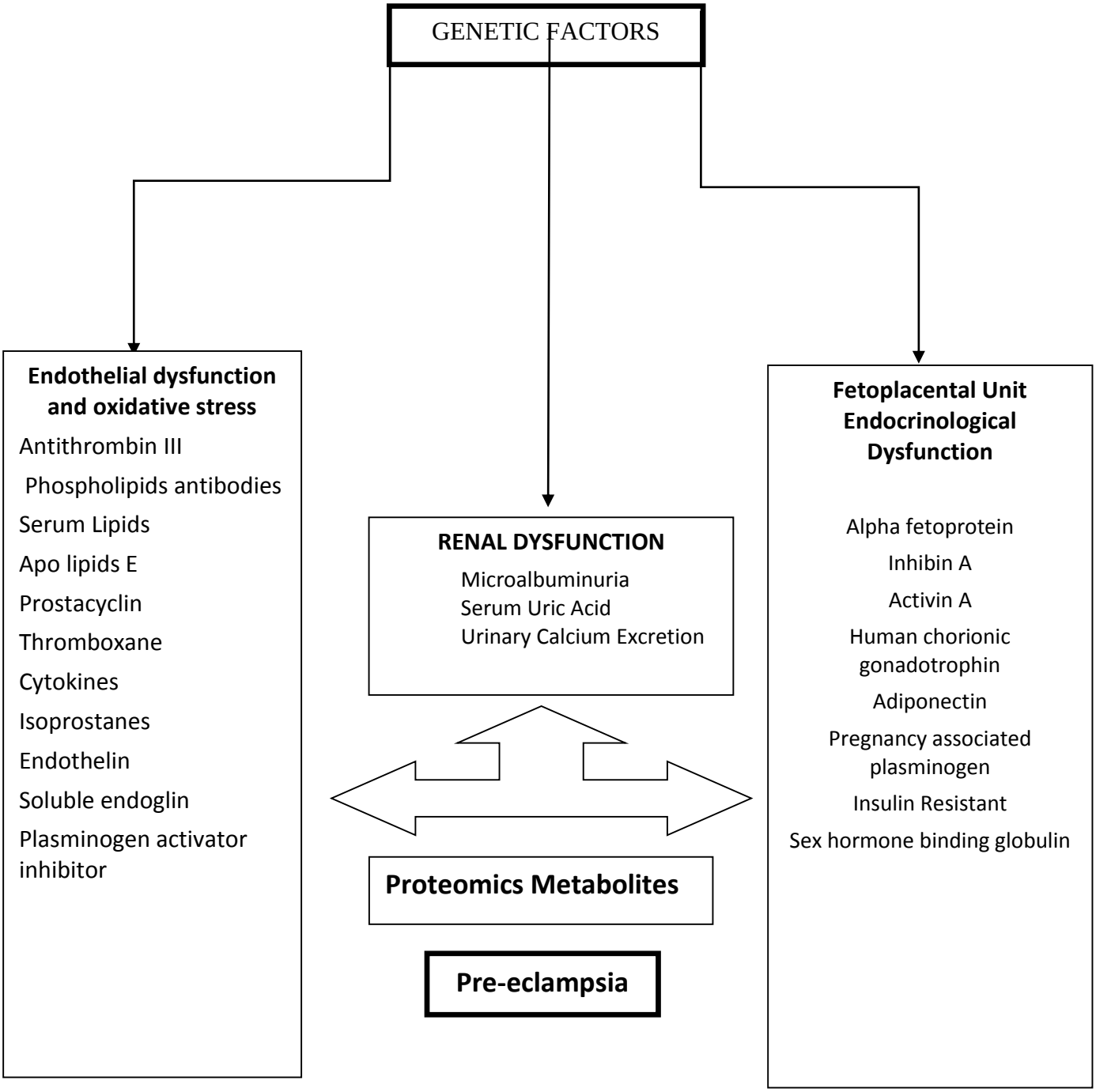

Figure: 10 Genetic factors responsible for Preeclampsia

10. Novel Biomarkers for Gestational Preeclampsia

10.1 Neutrophil-lymphocyte ratio in the disease

The assumed role of neutrophil-lymphocyte ratio in the serum concentration of the pregnant women have been explored and current evidence on the prediction of preeclampsia is found conflicting. The neutrophil-lymphocyte ratio has been considered most prompt and accessible biological marker for the detection of diseases related to sepsis. It has also found to be used in sub-clinical inflammation recognition. Experiments have been performed to analyze the normotensive women with gestation to compare and explore neutrophil-lymphocyte ratio value according with the data. NLR ratio is said to be calculated by dividing total number of neutrophil with total number of lymphocyte mostly from peripheral blood sample.

Enormous findings on meta-analysis predicted that NLR value is greater in women with preeclampsia especially in severe conditions. Neutrophil-Lymphocyte ratio is considered as a useful laboratory biomarker for clinical prediction and disease severity evaluation parameters of preeclampsia.

10.2 PAPPA and SE selectin

Women with early history of preeclampsia is at higher risk for developing cardiovascular disease. Hence, determination of pathophysiological mechanism of cardiac disease can be useful to eradicate the unwanted side effects. A study was conducted to measure the cardio vascular risk generator in women during 10 years of post-pregnancy period. This was predicted by elevated blood pressure (>90mmhg) and proteinuria (>0.3g/24hr) between 20 to 32 weeks of gestation.

Hypertension was more reported in women with post preeclampsia (42%) as compared to that in reference women (17%). Occurrence of diabetes mellitus, serum lipid biomarkers and inflammatory biomarkers like fibrinogen and CRP which were same in both the cases. Through data, one can predict that women with 10 years after preeclampsia have higher level of PAPPA and SE selectin than women without history of previous preeclampsia. Elevated levels of PAPPA and SE selectin contribute positive in development of risk factors in future related to heart.

SE selectin and PAPPA as a CVD biomarkers are indulged in early onset of preeclampsia and is associated with adjustments of CVD risk factors. Especially PAPPA can be an interesting unapproached biomarker for prediction or onset of any cardiovascular disease. It can be of core interest in elucidating the beneath mechanisms of preeclampsia and related cardio vascular disease. Future prospects lie in finding pathophysiological mechanisms of women with CVD and PE.

10.3 Inhibin A

Inhibin A is a glycoprotein mainly produced by cytotrophoblast of human placenta during pregnancy which is proven to be a reliable biomarker for prediction and evaluation of gestational preeclampsia depending on the level of severity. Studies postulated that Inhibin a level may increase than normal range as early as 10 to 15 weeks of pregnancy whereas maternal serum levels of inhibin A are 10 times higher in women with severe preeclampsia than normal or mild preeclamptic conditions. It was reported that the level of serum concentration of inhibin A is directly linked to early incidence of occurrence of disease and the estimated severity can be predicted.

10.4 Wiskott-Aldrich syndrome protein verprolin (WAVE2 protein)

WAVE2 is a protein that acts on actin cytoskeletal reorganization and lamellipodia protrusion formation, evolved in migration of cell and invasion process. Study was performed to check the connection of reactive oxidative species and WAVE2 protein in developmental stage of preeclampsia and to check whether expression of WAVE2 in trophoblast cells is vulnerable to oxidative stress. Conducted study observed reduction of WAVE2 protein and excessive generation of reactive oxidative species during preeclampsia. In addition, placental oxidative stress can be a result of fluctuation in oxidative concentration after hypoxia-reoxygenation (H/R) through the action of ROS.

11. Summary

Preeclampsia is a complication and metabolic syndromes observed in preeclamptic women and children at later stage of lifespan. Moreover, studies reflected presence of vasoactive substances like cytokines, radicles and peroxides in the system which escalates fatality of the condition that ends up with endothelial damage. Thromboxane prostacyclin disparity leads to progress in glomerular leak, activation of coagulation and aggregation which results in proteinuria and diffuse intranasal coagulation. Furthermore, uterine renin angiotensin-aldosterone causes sodium and fluid retention that leads to capillary leak contributing to edema whereas vasoconstriction elevates blood pressure of the body resulting in hypertension. Predisposition of hypertension and diabetes leads to failure in conversion of spiral arteries to vascular sinuses which provokes gestational ischemia due to placental production of thromboplastins leading to growth retardation of fetus if preeclamptic condition continues uninterrupted or untreated, eclamptic stage may occur. Volume of amniotic fluid, fetal muscle tone, fetal breathing can be examined by biophysical profiling. Antiplatelet therapy can be accessed before or after 15 weeks of gestation with low dose of aspirin to prevent morbility and fetality caused by preeclamptic stage on the foetus.Consumption of food bars containing L-arginine and antioxidant vitamins may prevent occurrence of preeclampsia during pregnancy.

12. Conclusion

Prevalence of eclampsia and preeclampsia amongst adolescent women is elaborated along with geographical details which can be useful to gather the information on occurrence. Though, accurate evidence on pathophysiology and pathogenesis of preeclampsia is still underway, few evidences are cumulated which can be reclaimable for future references. Presently, diagnosis and preventive measures are focused upon to mitigate preeclampsia in women at early stage of pregnancy together with variant pathological tests. Management strategies are devised according to severity of condition in a patient through non pharmacological and pharmacological measures. Further research on newly discovered biomarkers of gestational preeclampsia is warranted to broaden up the concept of actual origin of the disease.

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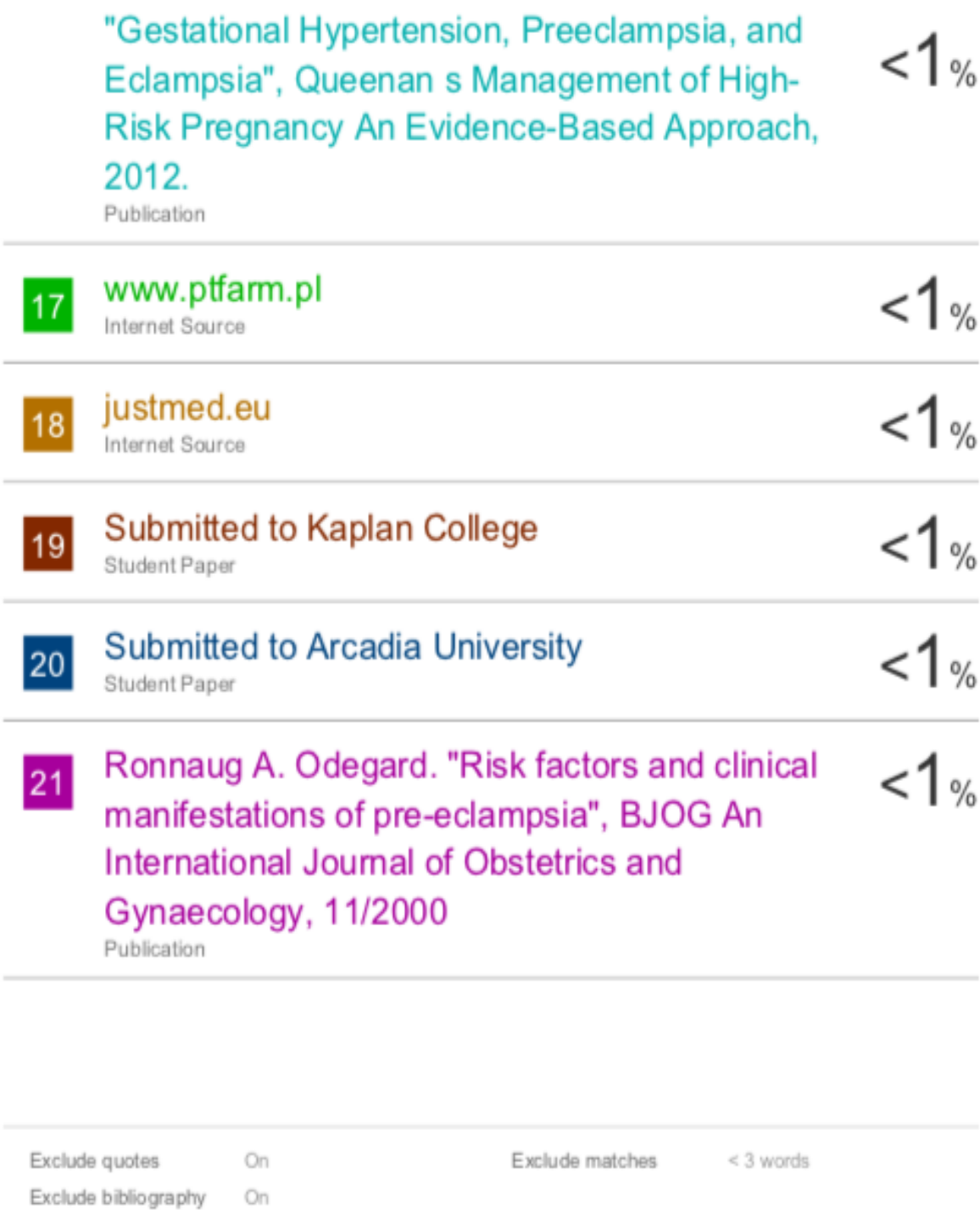

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