1-1 Introduction:

Doppler ultrasound can determine the presence or absence of blood flow and its direction, speed and character. Rapid scanning and processing of Doppler data allow color-coated presentation of Doppler information to superimposed on gray – scale atomic images. Doppler information is applied to loud speakers for audible evaluation and to chart recorder and spectral display for quantities analysis. Doppler instruments include sonographic imaging to determine the anatomic location from which the Doppler information is acquired (WHO, 2004).

The uterine artery is an artery that supplies the uterus. It spring from the anterior division of the hypogastria and runs toward the cervix about 2cm reaching the junction of the uterine tube and uterus (Koonin L.M, et al, 1997).

Pregnancies hypertensive disease is important case of maternal and fetal morbidity and mortality because chronic or severe hypertension in pregnancy leed to eclampsia or pre-eclampsia and also leed to intrauterine growth retardation.

Screening of uterine artery Doppler in early pregnancy specially in high risk patient may reduce the morbidity and mortality rate.

Risk of hypertension in pregnancy include eclampsia and pre-eclampsia are estimated to be responsible for proximately 14% of maternal death per year (50,000 – 75,000) in developing country (WHO, 2004).

Pre-eclampsia is important of pregnancy hypertension diseases it is the most common cause of maternal death (Eclampsia trail collaborative group, 1995) and first cause of maternal admission to intensive care unit (Tang L. C. et al, 1991).

Pre-eclampsia is pregnancy specific syndrome characterized by new honest hypertension and proteinurea, occurring usually after 20 weeks of gestational, although the etiology remain unknown, placenta hyperfusion and diffuse endothelial cell injury are considered to be the central pathologic event.

Pre-eclampsia is two types, mild and severe. It may leads to liver and renal failure, disseminated intravascular coagulopathy and C.N.S (Central Nervous System) abnormalities.

Pre-eclampsia is resolved by delivery. Previous study has shown that early and late honest associated with different biochemical and clinical feature although the early honest is almost invariable associated with placental insufficiency and growth restriction because of defective trophoplastic invasion the late honestis more prevalent in general and placenta involvement is minimally present in patient with early honest.

Pregnancies hypertension disease has expectant management and improve neonatal outcome in selected case and decrease neonatal intensive care unit and pittance and neonatal respiratory distress (Sibai B. M, et al, 1994).

Doppler ultrasound should be part of setup of every units. That provides antenatal medical service with good experience and well trained examiner.

Further researches should be also concentrate on combining uterine artery disease, ultrasound with other tests that used in clinical care. This may improve prediction accuracy and the clinical important value of test.

1-2 Problem of the study:

This study aimed to evaluate the prediction capacity of uterine artery Doppler ultrasound in first and second trimester in, in women who have history of pregnancy induced hypertension (PIH), and, or intrauterine growth restriction (IUGR), or unexplained prenatal fatal death in their previous pregnancies in order to reduce the feto-maternal morbidity and mortality.

1-3 General objectives:

- To determine the normal blood flow of uterine artery in the first and second trimester.
- To determine the changes in the uterine artery blood flow during first and second trimester as pregnancy in patient attending TurkishHospital- outpatient clinic.
- To predict (IUGR) and/ or early and late pre-eclampsia with the use of one step uterine artery screen during first and second trimester in high risk patient.

1-4 Specific objectives:

- To determine the changes in uterine artery blood flow abnormalities during first and second trimester (between 12 – 24 weeks) in high risk patient.
- To differentiate between types of intrauterine growth restriction.
- To predict early and late honset of preeclampsia.

1-5 Overview of the study:

The study includes five chapters; the first chapter includes the introduction, the problem of the study, general and specific objectives, and overview of the study. Chapter two covers definitions, diagnosis and managements of intrauterine growth restriction and preeclampsia, and explains the physiological changes that occur during pregnancy and the anatomy of the uterine artery. Chapter three covers the methodology for the obtaining data, material and techniques.

Chapter four summarizes the results of the study involving assessment of impedance to flow and changes to flow and changes in the uterine artery indices. Chapter five includes the results, discussion, conclusion and recommendations.

2. Background & Literature Review

Hypertension in pregnancy lead to risk like IUGR and preeclampsia and preeclampsia affects approximately 2 -3% of pregnancies and is a major contributor to maternal death with estimate of 50,000 death a year worldwide (World Health Organization, 1996).

Gestational hypertension systolic blood pressure used to diagnose pre-eclampsia

More than 140 mmHg or diastolic blood pressure more than 90 mmHg at least 2 occasions, 6 hours to 1 week apart and protein urea > 300 mg in 24 hours urine collection or dipstick measurement or more than 24 of new one after 20 weeks of gestation. In severe hypertension of pregnancies patients with preeclampsia were sub- classified as either early one after 20 weeks less than 34 weeks of gestational age. And late honest preeclampsia more than 34 weeks of gestation according to the gestational age at which preeclampsia was diagnose. Severe preeclampsia was defined as severe gestational hypertension systolic blood pressure of 160 mm Hg or greater and diastolic blood pressure of 110 mm Hg or greater and mild protein urea or mild hypertension and severe protein urea a 24- hour urine sample that contains more than 3-5 g protein or urine specimen of more than 3+ protein by dipstick measurement. Patient with an abnormal liver function test aspartate amino transferase more than7014/L and thrombocytopenia platelet count more than

100,000 cm^3 were also classified as having severe hypertension and severe preeclampsia.

Supper imposed preeclampsia defined as the development of protein urea> 0.3 g of protein in 24 hour urine collection or dipstick test result > 1+ after 20 weeks of gestation in patient with chronic hypertension (Redman CW, et al, 2005).

2-1 Pathophysiology:

2-1-1 Pathophysiology of sever hypertension:

The general consensus is that severe hypertension or pre-eclampsia is an endothelial cell disorder resulting in mid- to severe microangiopathy of target organ as brain, liver, kidney and placenta (Lainky, 2002), while hypertension maybe the most common presenting symptom. It should not be viewed as the initial pathogenic process. Evidence of the other organs involvement before hypertension becomes fulminant is not uncommon. Several circulating markers of endothelial cell injury have been shown to be elevated in women who develop preeclampsia before they become symptomatic. Evidence to date suggest that oxidative stress circulatory maladaptation; inflammatory; and humeral, mineral and metabolic abnormalities may all contribute to endothelial dysfunction and pathogenesis of severe hypertension and preeclampsia (Lainky, 2002).

Placenta hypo-perfusion or ischemia in pre-eclampsia has many causes. Pre-existing vascular disorders such as

hypertensions and connective tissue disorder can result in poor placental circulation, in case of multiple gestation or increase placenta mass. It is not surprising for the placenta to become under perfused. However, most women who have severe hypertension and develop pre-eclampsia are healthy and don't have underlying medical condition. In this group of women, abnormally shallow placentation has been shown to be responsible for placental hypo-perfusion.

Trophoplast is the ectoderm that develops into the human placenta. Differentiation of trophoplast yields on endovascular phenotype that invades the maternal vasculature during the first trimester and replace the smooth muscle normally present in the arteries with a none contractile matrix material. The physiological result of this normal destructive event is a high flow resistance vascular conduct. (Caniggia et al., 2000).In normal pregnancy impedance to flow in the uterine arteries decrease with increase gestation. Absence of trophoplast invasion of arterial sleeves a high resistance vascular with persistent smooth muscle histopathology of the maternal blood vessels. This result in an under- perfused placenta and fetal villi in the placenta that shown sign of injury. The latter findings are apparent in the placenta as from both IUGR and preeclampsia as Fibrin deposition (Owen P, et al, 2002).

2-1-2 Placentation in pre-eclampsia:

The shallow placentation noted in pre-eclampsia is result of the inability of trophoblasts to invade the decidual vessels. In normal pregnancies, a subject cytotrophoblasts called invasive cytotrophoblastsmigrate through the implantation. Site and invade decidua tunica media of maternal spiral arteries and replace its endothelium in a process called pseudo vascularization (Tylor RN, et al, 1998). Results of these changes, these vessels undergo transformation from small muscular arterioles to large capacitance, low- resistance vessels. This allows increase blood flow to the maternal-fetal interface, remodeling of these arterioles probably begins in the first trimester and end by 18 – 20 weeks gestation. However, the exact gestationalage at which the invasion stops is unknown. In patient who has been chronic hypertension and develop pre-eclampsia. This invasion of the deciduas arterioles is incomplete. The invasive cytotrophoblast fail to replace tunica media, resulting in mostly intact arterioles that are capable of vasoconstriction. Histological evaluation of the placental bed demonstrates few cytotrophoblasts beyond the decidual layer.

2-2 Epidemiology and risk factor:

The incidence of pre-eclampsia in the United States is estimated to range from 2- 6% in healthy nulliparous women (Redman CW, et al, 2005). In the developing world, the incidence is reported to be 4- 18% (Friedman SA, et al 1995).

The disease is mild in 75% of cases and severe in 25% (Germain SJ, et al, 2007) of all cases of pre-eclampsia, 10% occur in pregnancies of less than 34 weeks gestation, eclampsia is estimated to occur in 1 in 200 cases of pre-eclampsia when magnesium prophylaxis is not administered (Taylor RN, et al, 2003).

The incidence is higher in women with history of pre-eclampsia, multiple gestation. Chronic hypertension and underlying renal disease in addition, obesity, diabetes, thrombophilia and age older than 40 years are risk factors put a woman at increased risk developing pre-eclampsia.

Some risk factors contribute to poor placentation while others contribute to increase placental mass and poor placental perfusion secondary to vascular abnormalities.

2.3 Classifications:

The National High Blood Pressure Education Program (NHBPEP) working group classifies hypertensive diseases in pregnancy into 4 groups: chronic hypertension, pre-eclampsia, pre-eclampsia in super imposed on chronic hypertension, and gestational hypertension. (Thadhanir M. W, et al, 2004).

The classification of hypertensive diseases in pregnancy according to the NHBPEP working group is as follows: (Levine R J, et al, 2006)

- Gestational hypertension: BP of 140/ 90 mmHg or greater for the first time during pregnancy, no protein urea and BP return to normal less than 12 weeks postpartum.

- Chronic hypertension: BP 140/90 mmHg or greater before pregnancy or diagnosed before 20 weeks gestation not attributable to gestational trophoblastic disease or hypertension first diagnosed after 20 weeks gestation and persistent after 12 weeks postpartum.

- Pre-eclampsia / eclampsia: BP of 140/ 90 mmHg or greater after 20 weeks gestation in a woman with previously normal blood pressure and with proteinuria (70.3g) protein in 24- hours urine specimen) eclampsia is defined as seizure that cannot be attributable to other causes in a woman with preeclampsia.

- Super imposed pre-eclampsia (on chronic hypertension): New honest proteinuria (> 300 mg/ 24 H) in women with hypertension but no proteinuria before 20 weeks gestation. sudden increase in proteinurea or blood pressure, or platelet countless than 100,000 in women with hypertension and protein urea before 20 weeks gestation. Mild pre-eclampsia is define as the presence of hypertension BP ≥ 140/ 90 mmHg) on 2 occasions, at least 6 hours apart protein urea is define as the presence of greater than or equal to protein or random dipstick or at least 300mg of protein in 24 – hour urine collection some

investigations and clinicians have accepted a urine protein – creatinine ratio of a least o.3 as criteria for protein urea, but the American College of Obstetricians and Gynecologists (ACOG) has not yet incorporated this in their definition (Ventatesha S, et al, 2006) edema and hyper reflexia are no longer consider to be diagnostic criteria. In addition, the relative rise of systolic blood pressure by 30mm Hg and/ or diastolic by 15 mmHg has been dropped from the criteria for hypertension

- severe pre-eclampsia : is defined as the presence of one of the following syrup torus or signs in the presence of pre-eclampsia, systolic BP of 160 mmHg or higher or diastolic BP of 110 mmHg or higher on 2 occasions at least 6 hours part proteinuria more than 500 mg in 24 hour period, pulmonary edema, oliguria (< 400 mL in 24 h) persistent headaches, epigastric pain, under impaired liver function thrombocytopenia.

- HELLP syndrome: (Hemolysis, elevated liver enzyme, low platelets) is a form of severe pre-eclampsia that has been associated with particularly high maternal and prenatal morbidity and mortality and may be present without hypertension or, in some occasions without proteinuria.

2.4 Diagnosis of pre-eclampsia:

Pre-eclampsia is diagnosed when new-honest hypertension and proteinuria are present in pregnant women according to the

criteria described in classification, because the clinical manifestation of pre-eclampsia can be nitrogenous, diagnosing pre-eclampsiamay not be straight forward. In particular, since the final diagnosis of gestational hypertension can only be made in retrospect, a clinician may be forced to treat some women with gestational hypertension as if she has pre-eclampsia. In addition to if a woman has underlying renal or cardiovascular disease, the diagnosis of pre-eclampsia may not become clear until the disease become severe.

Hypertension is diagnosed when 2 blood pressure readings of 140/ 90 mmHg or greater are noted 6 hours a part within one-week period, measuring BP with an appropriate sized cuff placed on the right arm at the same level as the heart is important. The patient must be sitting and ideally, have had a chance to rest for at least 10 minutes prior to the BP measurement, she should not be lying down in lateral decubitus position since the arm of used to measure the pressure in this position will be above the right atrium (ACOG Technical Bulletin, 1996).

To diagnose proteinuria, 24 hour urine collection for protein and creatinine should be obtained whenever possible. Up to 30% of women with gestational hypertension who have trace protein noted on random urine samples may have 300 mg of protein in 24 hour urine collection (ACOG Committee on practice

Bulletin, 2001). The 24 hour urine protein analysis remain the criterion standard.

Furthermore, HELLP syndrome has been known to occur without hypertension or proteinuria, because the underlying pathophysiology of pre-eclampsia is diffused. Endothelial cell disorder influencing multiple organs, hypertension does not need to necessarily precede other symptoms or laboratory abnormalities. Presenting symptoms other than hypertension may include edema, visual disturbances, headache, and epigastric or right upper quadrant tenderness. All women who present with new honest hypertension should have the following laboratory tests: complete blood count (CBC), serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, serum creatinine, and uric acid, in addition, a peripheral smear, serum lactate dehydrogenase (LDH) level measured, and direct bilirubin should be done if HELLP syndrome is suspected, while coagulation profile pt, and fibrinogen should also be evaluated. The clinical use of platelet count is 100,000 or more with no evidence of bleeding (Sibai BM, 2003). The differential diagnosis for HELLP syndrome must include various causes for thrombocytopenia and liver failure such as acute fatty liver of pregnancy, hemolytic uremic syndrome, acute pancreatitis, fulminant hepatitis, systemic lupus, erythematous, cholecystitis, and thrombotic thrombocytopenic purpura (Vattern LJ, et al, 2004).

Eclampsia:

Define as new honest tonic- colonic seizure in an otherwise healthy women with hypertensive disorder of pregnancy, is significant complication of pre-eclampsia and is associated with high maternal and neonatal morbidity and mortality, multiple studies have described various abnormalities noted on CNS imaging studies. Both CT and MRI scans have revealed numerous abnormalities such as cerebral edema, focal infraction, intracranial hemorrhage, and posterior leuko-encephalopathy (Villar J, et al, 2001).

2.5 Management of preeclampsia:

The optimal management of a woman with preeclampsia depends on gestational age and severity of the disease. Since delivery is the only cure for the preeclampsia, clinicians must try to minimize maternal risk while maximizing fetal maturity. The primary objective is the safety of the mother and taken delivery of healthy new born. A pregnancy complicated by mild pre-eclampsia at or beyond 37 weeks should be delivered while the pregnancy outcome is similar in these women as those with normotensive pregnancy, the risk of placental abruption and progression to sever disease is slightly increased (Sibai BM, 2004). Thus, regardless of cervical status, induction of labor should be recommended cesarean section may be performed base or standard obstetric criteria.

Prior to 37 weeks expectant management is appropriate in most cases, patient should be hospitalized and monitored carefully for the development of worsening of pregnancies hypertensive or pre-eclampsia or complicated of pre-eclampsia, Anti partum testing is generally indicated during expectant management of these patients. However, the types of tests to be used and the frequency of testing have little consensus. Most clinicians offer anon stress test (NST) and biophysical profile (BPP) at the time of diagnosis and usually twice per week until delivery (Livingston JC, et al, 2003).

2.5.1 Chronic hypertension and severe pre-eclampsia:

Chronic hypertension lead to aclampsia and severe pre-eclampsia is diagnosed after 34 weeks gestation, delivery is most appropriate. The mode of delivery should depend on severity of the hypertension disease and likelihood of successful induction, however, whenever possible, vaginal delivery should be attempted and cesarean section should be reserved for routine obstetric indications patient presenting with severe, unremitting headache, visual disturbance, and right upper quadrant tenderness in the presence of hypertension and/ or proteinuria should be treated with at most caution.

2.5.2 Expectant management of chronic hypertension and severe pre-eclampsia:

If patient presents chronic hypertension and severe pre-eclampsia before 34 weeks gestation, but appears stable and

fetal condition is resuming expectant management may be considered only in tertiary center in addition because delivery is always appropriate for the mother, some authorities consider delivery as the definitive treatment regardless of gestational age. However, delivery may not be optimal for fetus that is extremely premature, therefore, in carefully chosen population, expectant management may benefit the fetus without greatly compromising maternal health.

All of these patients must be evaluated on labor delivery unit for 24 hours before a decision for expectant management can be made. During this period, maternal and fetal evaluation must show that the fetus does not have severe growth restriction for fetal distress in addition; maternal urine output must be adequate. The women must have essentially normal laboratory values (with the exclusive exception of mildly elevated liver function test results less than 2 time the normal value and hypertension that can be controlled.

Fetal monitoring should include daily nonstress test and ultrasonography performed to monitor for the development of oligohydramnios decreased fetal movement, in addition fetal growth determination at 2-week intervals must be performed to document adequate fetal growth. In addition, a 24- hour urine collection for protein may be repeated corticosteroids for fetal lung maturity should be administered prior 34 weeks (Lykke JA, et al, 2009).

Daily blood tests should be performed for LFTs, CBC, uric acid and LDH patients should be instructed to report any headache, visual change, epigas trick pain or decreased fetal movement.

2.5.3 Seizure prophylaxis:

Magnesium sulfate is the drug of choice for seizure prophylaxis in women with preeclampsia although the precise mechanism of it is anti- seizure activity is unknown several randomized studies, showed that magnesium sulfate is better than benzodiazepam or phenytoin in preventing the honest of initial eclamptic seizure and recurring seizures (Hauth JC, et al,.). Therapy is started at the beginning of labor or prior to cesarean section and continued 24 hour postpartum in most cases, magnesium sulfate therapy for seizure prophylaxis should be administered to all women severe hypertension and severe preeclampsia during induction or labor. However prophylaxis for mild preeclampsia is controversial ACOG recommended magnesium sulfate in severe preeclampsia (Lykke JA, et al, 2009).

2.5.4 Acute treatment of severe hypertension in pregnancy:

Systolic blood pressure of 160 mmHg or greater and/ or diastolic pressure around 140/ 90 mmHg. Hydralazine is direct peripheral arterial or vasodilator and in the past was widely used as the first line treatment for acute hypertension in pregnancy

(Waugh JJ, et al, 2003). Hydralazine has a slow of action 10–20 min and peaks approximately 20 minutes after administration. Hydralazine should be given as in bolus at a dose of 5 – 10 mg depending on the severity hypertension; it may be administered every 20 minutes up to maximum dose of 30 mg. The side effects of hydralazine are headache, nausea and vomiting, importantly hydralazine may result in maternal hypertension, which may subsequently result in a non-reassuring fetal heart ratio tracing in the fetus (Durnwald C, et al, 2003). In a recent meta- analysis, Magtt et al, pointed out that hydralazine was associated with maternal prenatal outcomes than labetalol and nifedipine (Naden RP, et al, 1985).

2.5.5 Eclampsia seizum:

When Eclamatic seizure occurs, maternal injury must be prevented. The airway must be protected and oxygenation assured, including placenta of supportive airway. If necessary to prevent aspiration, management may include placenta of padded tongue blade, and suctioning of the oral cavity, pulse oximetry should be performed to monitor oxygenation and oxygen by face mask should be provided (Chesley LC, 1978). Fetal monitoring may be instituted when the maternal airway and seizures are under control, since intervention for the fetus should not be considered until the mother's condition is stabilized. Magnesium sulfate must be administered to prevent further seizure activity. A loading dose of 4-6 g followed by maintenance dose of 2g/h is

given of women with eclampsia 10% will have second convulsion after receiving magnesium sulfate (Fisher KA, et al, 1981), occasionally convulsion may recur even though patient receives adequate dose of magnesium sulfate in these patients, sodium amobarbital, 250 mg IV over 3-5 minutes may be administered (BM. Diagnosis, 2004).

2.5.6 Postpartum management:

Pre-eclampsia resolves after delivery, however, patient may still have elevated blood pressure postpartum. Liver function test and platelet count must be performed to document decreasing values prior to hospital discharge. In addition, one third of seizures occur in the postpartum period, most within 24 hours of delivery, and almost all within 48 hours (BM. Diagnosis, 2005). Therefore, magnesium sulfate seizure prophylaxis is continued for 24 hours postpartum, in addition, use of dexamethasone (10 mg IV 6- 12 h for 2 doses followed by 1mg IV 6- 12 h for 2 doses) has been proposed in the postpartum period to restore platelet count to normal range in those with persistent thrombocytopenia (Buchbinder A, et al, 2002).

Elevated blood pressure may be controlled with nifedipine or labetalol postpartum if patient is discharge with blood pressure medication, reassessment and blood pressure check should be performed at the latest one week after discharge, numerous screening tests for pre-eclampsia has been proposed over the past few decades. A screening test should be safe, valid, reliable,

acceptable to the population, reproducible appropriate for the population and economical pre-eclampsia is an appropriate disease to screen as it is common, important, and increase both maternal mortality and prenatal mortality (Sibai BM, et al, 2007).

Currently, the clinical value of an accurate predictive test for pre-eclampsia is not clear since we lack effective prevention, intensive monitoring in women who are at increased risk developing pre-eclampsia, when identified by predictive test, may lower the incidence of adverse outcome for both mother and the neonate, however, the effectiveness of such a strategy must be rigorously investigated.

2.6 Recurrence

In general the recurrence risk of pre-eclampsia in women whose previous pregnancy was complicated by pre-eclampsia near term is approximately 10% (Sibai BM, 2004). If a woman had severe pre-eclampsia including HELLP syndrome and/ or eclampsia, she has 20% risk of developing pre-eclampsia sometime in her subsequent pregnancy (Wltin AG, et al, 1998). If a women had HELLP syndrome or eclampsia, the recurrence risk of HELLP syndrome and eclampsiaare 5% (Mageo LA, et al, 2003), and 2% (Creasy RK, et al, 2004), respectively, the recurrence ratio rises the earlier the disease manifested during the index pregnancy. If preeclampsia presents clinically before

30 weeks gestation the recurrence ratio may be as high as 40% (Martin JN JR, et al, 2003).

2.7 Intrauterine growth restriction (IUGR)

Acceptable reference standards for intrauterine growth restriction included birth weight below 10th centile adjusted for gestational age and base on local population value reference in the medical literature to underweight infants date 1919, when it was suggested (Bernstein I, et al, 1996) that, all new born weighting less than 2,500g (5lb, 8oz) should be classified as "premature" however, it was not until 1961 that the World Health Organization (WHO) of birth weight is a weight less than 2,500g (5lb, 8oz) or below the 10th percentile gestational age, low birth weight includes two pathogenic conditions and are normal conditions. The normal condition refers to the healthy but constitutionally small baby. The pathologic conditions include preterm delivery and intrauterine growth retardation (IUGR). In the United States, (IUGR) is linked to an increase of six to 10 times in prenatal mortality (Creasy RK, et al, 1994).

2.7.1 Epidemiology

According to the common definition of (IUGR) as birth weight under 10th percentile, the expected incidence of (IUGR) should be 10 percent. The actual incidence however, is only about 4 to 7 percent about one fourth of infants who are below the 10th percentile have normalized birth weight when it is corrected for low maternal have a normalized birth weight when it is

corrected for low maternal weight, maternal phenotype or residence at higher latitude (Gardosi J, et al, 1992). Some regional variation in birth weight may exist within the United State and Canada. Previously published standard found variation of 100 to 200 (3.5 to 9 oz) when comparing 10th percentile infant of the same gestational age who were born in Canada with those born in Denver California (Creasy RK, et al, 1994).

The approximately 3.5 million annual births in the United States translate to about 350,000 infants who are born weighting less than 2,500g (5lb, 8oz). approximately one third of these infants, about (100,000) have true (IUGR), and the remaining two third (about 250,000) are constitutionally small (Creasy RK, et al, 1994). Some authors apply the term "small for gestational age" To the latter group of infants, most authorities prefer to maintain the strict and more inclusive definition of (IUGR) as less than 10 percent of predicted fetal weight for gestational age using the 10th percentile as standard results in over diagnosis of (IUGR). Other authors, however, have suggested using the 5th percentile to define IUGR infant (Bernstein I, et al, 1996).

The counter argument in fever of strict definition is that birth weight is probably the single most important factor affecting neonatal morbidity and mortality and should be aggressively screened for (Gardosi J, et al, 1992). A lack of consensus among primatologists makes it difficult to fully define the extent of (IUGR) and the subsequent effectiveness interventions.

2.8 Etiology

Many different factors cause (IUGR), but they may be divided into two large categories, based on Etiology. These categories include fetoplacental factors and maternal factors, within the categories of maternal and fetoplacental factors are many specific causes.

Historically (IUGR) has been categorized as asymmetric. Symmetric (IUGR) refers to fetuses with equally poor growth velocity of the head, the abdomen and the long bones. Asymmetric (IUGR) refers to infants whose had and long bones are spared compared with their abdomen and viscera. It is now believed that most (IUGR) is a continuum from asymmetry (early stages) to symmetry (late stage). Maternal cause of (IUGR) account for most utero-placental cases. Chronic hypertension is the most common cause of IUGR moreover; the infants of hypertensive mothers have a three- fold increase in prenatal mortality compared with infant with (IUGR) who are born of normotensive mothers because of their significant risks. One author (Pijneborg RT, et al, 1980) recommends delivering these infants by 37 weeks of gestational age. Pre-eclampsia cause placental damage that results in uteroplacental insufficiency, the pathogenic mechanism is thought to be a failure of trophoblastic invasion by maternal spiral arterioles by 20 to 22 weeks of gestation (Bernstein I, et al, 1996). This failure causes luminal narrowing and medial degeneration

leading to diminished blood flow to the developing infant consequently; these infants fail to grow normally, infectious causes of fetal growth delay account for about 10 percent of all cases of IUGR. These causes include (TORCH) group: toxoplasma gondii, rubella, cytomegalovirus and herpes simplex virus types 1 and 2 other potential pathogenesis include hepatitis A and hepatitis B, human immunodeficiency virus (HIV) and treponema palladium (symphilis).

Maternal prepregnancy weight and weight again during pregnancy are considered strong indicator of birth weight (Piper JM, et al, 1996), during World War II, population of women in Leningrad who underweight prolonged malnutrition delivered infant with an average birth weight of 400 to 600g (14 to 21oz) less than expected.

In lateral study of Guatemalan Indian (Abrams BF, et al, 1986), it was found that protein malnutrition occurring before 26 weeks of gestation resulted in IUGR. The current consensus is that maternal weight of less 10kg (22lb) by 40 weeks of gestation is clearly risk factor for IUGR (Creasy RK, et al, 1994).

Normal smoking may be the cause of 30 to 40 percent of cases of (IUGR). One study (Lechtig A, et al, 1975) found a dose dependent decrease in fetal weight with an increasing number of cigarettes. Smoked each day (7.4g (0.26oz) decrease for each cigarette smoked per day).

Another study found that women who smoked 11cigarettos or more cigarettes daily had infant weighting 330g (11.5oz) less than predicted and measuring 1.2cm shorter than control subjects.

Early use of alcohol by the pregnant mother may lead to fetal alcohol syndrome, while second or third trimester use may result in (IUGR). As little as one to two drinks per day have been shown to result in growth delayed child (Dougherty CR, et al, 1982).

Intra uterine growth retardation occurs 10 times more frequently in twin deliveries than in single gestation. The incidence of (IUGR) in twin is about 15 to 25 percent (Piper JM, et al, 1996). Decreased birth weight is second only to respiratory distress syndrome as cause of infant mortality in twins. Reasons for IUGR in twin pregnancies include poor placental implantation, placental crowding and twin-to-twin transfusion.

2.9 Diagnosis

Before the development of Ultrasonography, delay fetal growth was indicated by low maternal weight gain, and fundal height measurement.

Currently, (IUGR) is still open suspected on the basis of fundal height measurement, a significant lake in fundal height is a 4 cm or greater difference than expected for gestation age. However, even carefully performed fundal height measurements only have 26 to 16 percent sensitivity in predicting IUGR

(Pijbebarg R, et al, 1980). (IUGR) is frequently detected in pregnancy with a less than expected third trimester weight gain (100 to 200g) (3.5 to 7oz) per week or as an incidental finding on ultrasound examination when fetal measurements are smaller than expected for gestational age.

The main prerequisite for determining (IUGR) is precise dating. The most accurate dating method uses ultrasound examination of 8 to 13 weeks. Later ultrasound examinations are helpful, but the margin of error is increased. The date of the last menstrual period, early uterine sizing and detection of fetal heart tones are helpful ways to accurately date the pregnancy most cases of (IUGR) present during third trimester, which makes them difficult to accurately diagnose. This is especially true if the patient has presented for prenatal care at a late stage. The physician must determine if the dating incorrected for prenatal and the fetal size is actually normal or if the mother truly needs further evaluation for (IUGR).

When the suspicion of (IUGR) is strange complete assessment of maternal risk factors should be undertaken. This includes past medical and obstetric history, medication use, recent infections, occupational or toxic exposure, and history of tobacco, alcohol or illicit drug use. Ultrasonography is normally the first study done to assess IUGR. This test loses its accuracy as the pregnancy progress, but the sensitivity predictive value can be improved if several variables combined (Nilsen ST, et al, 1984).

These variables include estimated fetal weight, head circumference and abdominal circumference. Estimated fetal weight is the most common screen. It is based on the measurements of head circumference, abdominal circumference and femur length; these measurements are plotted on preexisting standardized chart. In about 95 percent of case ultrasound examination allows an estimation of fetal weight with a 15 to 18 percent variable (Mills JL, et al, 1984). An estimated fetal weigh of less than the six percentile strongly correlates with growth retardation and an estimated fetal weight of greater than the 20th percentile virtually rules out (IUGR). An estimated fetal weight at the 15th percentile or less, or a decreasing estimated fetal weight as determined by serial ultrasound examination, is suggestive of (IUGR). In all growth retarded fetuses, the abdominal circumference is the first biometric measure to change. This translates to an increase ratio of head circumference to abdominal circumference (AC). The ratio of head circumference (HC) to abdominal circumference is normally one at 32 to 34 weeks and falls below one after 34 weeks. A ratio of greater than one detects about 85 percent of growth- restricted fetus (Pijnenborg R, et al, 1980).

The first radiographic sign of (IUGR) may be decreased amniotic fluid volume. About 85 percent of (IUGR) infant have oligohydramnios (Barker DJ, 2004). This condition occurs because blood flow from peripheral organ (kidneys) is delivered

to the brain renal perfusion and urinary flow rates are commonly reduced in infants with (IUGR) (Steel SA, et al, 1988). An amniotic fluid index of less than 5cm increases the risk of (IUGR). A vertical pocket of amniotic fluid less than 1 cm regardless of gestational age, is found in about 39 percent of cases of IUGR (Tylor RN, et al, 1998).

2.10 Role Doppler assessment in (IUGR):

Maternal arterial umbilical blood flow increases from 50 ml per minute early in pregnancy to about 700 ml per minute at term. The increase is secondary to gradual decrease in vessel resistance to blood flow throw out the pregnancy. Doppler velocimetry uses ultrasound to measure peak- systolic and end-diastolic flow through the umbilical artery. Three measurements are averaged as the systolic/ diastolic ratio. As the pregnancy progresses, diastolic flow increase, and the systolic ratio should gradually degrease. In a large number of (IUGR) pregnancies, an alteration in placental blood flow occurs. As a result, researches have correlated on increased systolic/ diastolic ration with (IUGR). The ratio is increased in about 80 percent of cases of(IUGR) diagnose by ultrasound examination (Doubilet PM, et al, 1995). An average systolic/ diastolic ratio greater than three at 30 or more weeks of gestation has a sensitivity of 78 percent and specificity 85 percent in predicting (IUGR) (Hadlock F, 1994).

Doppler velocimetry, previous discussed as diagnostic technique for IUGR, has not found a place in routine antenatal surveillance. It has helped physicians understand the pathophysiology of IUGR with regard to diminished blood flow. Results of this procedure correlate with increase fetal morbidity and mortality, an absent or reversed end diastolic umbilical flow is an ominous finding and necessitates aggressive intervention. As screening test, however, the procedure appears to be lacking in benefit, some studies have had normal Doppler velocimetry result just before birth (Queenan JT, 1994). Currently, the American College of Obstetrics and Gynecology classifies fetal Doppler studies as investigational diagnostic studies used in the evaluation of (IUGR) (Veille JC, 1989). Ultrasonographic placental grading has been studies with respected to (IUGR).

Normally, a grade 3 or mature placenta would not be detected before 36 weeks of gestation. The presence of a grade 3 placenta before 36 weeks, along with an estimated fetal weight of less than 2,700g (5lb, 14oz), carries four- fold risk IUGR (Friedman SA, et al 1995).

2.11 Antenatal surveillance

When the diagnosis of IUGR has been established, it's helpful to determine a specific etiology. The therapy may be nonspecific but should try to address the underlying cause. Many infants thought to be growth- retarded are, in retrospect, found to be constitutionally small. The key management uses are the

gestational age of the pregnancy to expedite delivery. Most fetal death involving (IUGR)occur after 36 weeks of gestation and before labor begins (Bernstein I, et al, 1996), the clinician must balance the risk of delivering a premature infant against the potential intrauterine demise.

Ultrasonography at three- to four- week intervals is recommended to assess fetal growth (58 -63).

It is important that the physician communicate with the ultra sonographer, indicating that suspected (IUGR)is the reason for serial examination appropriate attention must be given to estimated fetal weight,(BPD) bipariatal diameter, (AC) head circumference, (AC) abdominal circumference and amoniotic fluid volume. Third trimester fetal weight gain should be 100 to 200g (3lb, 80oz to 7lb) per week. Head circumference that does not change over four- week period is worrisome and may be an indication for prompt delivery (Bernstein I, et al, 1996).

Twice- weekly nonstress testing (NST) is an appropriate surveillance method in following a fetus with IUGR. A reactive NST (two acceleration in fetal heart ratio of more than 15 beats per minute lasting for more than 15 second in a 20 minute span) has been shown to correlate with fetal wellbeing (Bernstein I, et al, 1996).

Spontaneous variable acceleration in fetal heart rate on the NST may indicates possible fetal hypoxemia and should be followed by contraction stress or a biophysical profile, the

biophysical profile include an NST- fetal breathing movement, gross body movements, fetal tone, and amoniotic fluid index. Two large studies (Kazzi GM, et al, 1983) found the biophysical profile to be predictive of fetal well- being fetal distress and ultimate prenatal mortality.

2.12 Treatment

Treatment of mother and the growth – restricted fetus is, when possible, dictated by the etiology of the condition. As previously noted, many of the conditions responsible for IUGR are not a may able to antenatal therapy.

2.12.1 Prenatal management:

Maternal hyper oxygenation has been evaluated in several studies, but only limited data prove its efficacy. In one study (Manning FA, et al, 1987), Nasal oxygen at 2, 5, 1 per minute administered to mother at 27 to 28 weeks of gestation improved neonatal blood gas measurements but resulted in an increased incidence of hypoglycemia and thrombocytopenia in the infants, one report (Redman CW, et al, 2005) suggests that supplemental oxygen may have a role in short term prolongation of pregnancy, while steroids can be administered to accelerate fetal lung maturity.

Low dose aspirin (150 mg per day) as treatment for IGUR has been studied over the past several years. One study (Manning FA, et al, 1993) found that when aspirin was given to women in the third trimester who had abnormal umbilical Doppler indices,

fetal weight and head circumference parameters were improved compared. Birth weight was improved and no excess of maternal or fetal aspirin related side effects occur.

2.12.2 Labour and delivery management:

Approximately one half of infants with IUGR haveintrapartum as physion and lower Apgar score than control subjects. A higher incidence of meconium aspiration has also been noted in these infants. Therefore, continuous monitoring of fetal heart rate throughout labors recommended in cases of (IUGR) (Piper JM, et al, 1996). Amnioinfusion may also have a role in these cases especially in the presence of oligohydramnios. Late declarations are more predictive of fetal hypoxia and resultant adverse outcome in this group of high risk infant. A lower threshold further choice of cesarean section is therefore recommended, neonatal resuscitation and subsequent care of the growth –restricted infant should follow in the same manner used with other new born problems to closely watch out far in infant with (IUGR)include hypoglycemia, hypocalcaemia, polycythemia secondary to intrauterine hypoxia and hypothermia due to decrease body fat (Bernstein I, et al, 1996).

2.12.3 Neonatal outcomes:

In most cases, infants with IUGR ultimately have good outcomes with reported mortality rate of only 0.2 to 1 percent, these infants often exhibit fast catch- up growth in the first three months of life and attain normal growth curves by one year of

age. Some early studies (ACOG technical bulletin no. 1994) have found variety of long term complications infants with IUGR. These complications include hyperactivity, clumsiness and poor concentration. Other studies (Ribbert LS, et al, 1991) have found growth retarded infant to be increase risk for development of hypertension, abdominal obesity and type 2 (noninsuline- dependent) diabetes as adult.

In recent British study (Uzan S, et al, 1991), records of 1,576 men and women born between 1920 and 1943 for whom birth weight and anthropomorphic measurements were recorded in detail after birth were examined. No definite association was found between cognitive function (intelligence quotient and vocabulary) and birth weight head circumference ratio of head circumference to abdominal circumference, collectively developmental studies demonstrate that many factors contribute to the ultimate intellectual development in infant growth with (IUGR), including birth weight, time of honest of IUGR head circumference, gestational age at deliver, etiology of the IUGR and post-natal environment, most infants with IUGR have excellent long- term prognosis.

2-13 Anatomy of uterine artery:

Theuterine artery is a branch of anterior division of the internal iliac artery, and divides further into four arcuate arteries, each of which divided into more than 25 spiral arteries. There are,therefore, between 100 and 200 spiral arteries which inter

the intervillous space. Two are arteries present,one on the left and the other on the right side of the uterus. Blood from the uterine arteries supplies blood to the muscles of the uterus and the placenta (Pijneborg RT, et al, 1980).

The blood supply to the uterus comes mainly from the uterine arteries with small contribute from the ovarian arteries. These vessels anastomose at the corner of the uterus and give rise to arcuate arteries that run circumferentially round the uterus. The radial arteries arise from arcuate vessels and penetrate at right angle into the outer third of the myometrium. These vessels give rise to basal and spiral arteries which nourish the myometrium, decidua, and the intervillous space of the placenta during pregnancy respectively. There are 100 functional opening of spiral arteries into the intervillaus space of mature placenta.

The uterine artery that originate from the internal iliac vessels approach the uterus at the level of the internal os. They ascend lateral to the uterine body and give of branches, which penetrate the myometrium. These branches then divided into so-called arcuate arteries which form a mesh throughout the outer myometrium. From these, radial arteries are directed to the endometrium and are visualized within the inner two third of the myometrium. They pass through the myometrium and become the spiral arteries whose vessels wall become invalid by trophoplast during pregnancy. Due to this process, the spiral arteries become wide and non-contractible channel and

complain low resistanceintervillous circulation develop this process impaired in hypertension or pre-eclampsia.

Figure (2-1): The uterine artery and its course
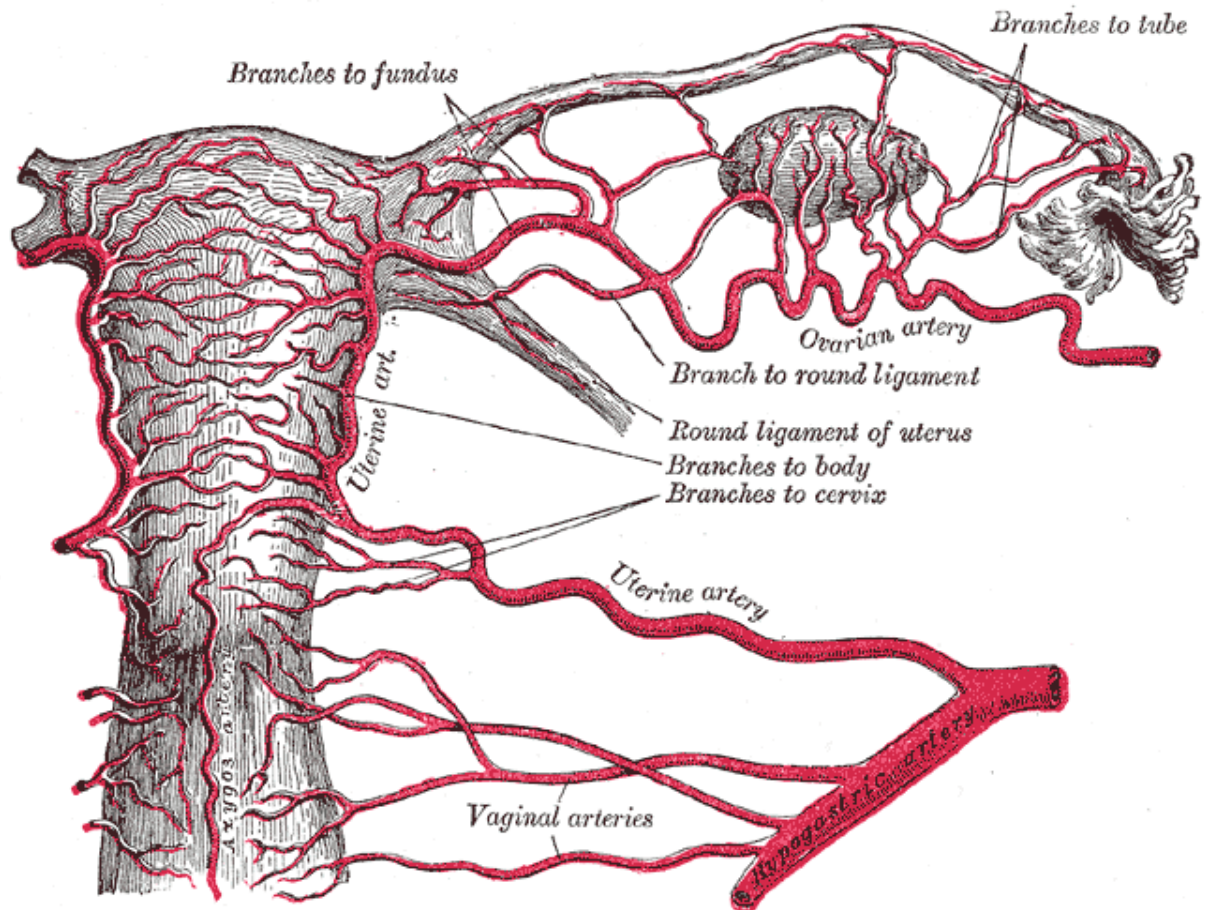
2-14 Physiological change during pregnancy:

Physiological modification of the spiral arteries is required to permit the tenfold increased in the uterine blood flow which is necessary to meet the respiratory and nutritional requirement of the fetus and placenta.

Brosenset. et. al., examined microscopically several hundred placenta bed biopsis, seven cesarean hysterectomy specimens

and two intact second trimester (Roberson CM, et al, 1990). Basal arteries showed no change, but spiral arteries were invaded by cytotrophoblast cells and were converted into utero placental arteries. These have diluted and tortuous lumen, a complete absence of muscular and elastic tissues, no continuous endothelial lining moral thrombi and fibirnoid deposition noted.

This conversion of the spiral arteries to utero placental arteries is termed "physiological change". It has been reported to occur in two stages: The first wave of trophoblastic invasion converts the decidual segments of spiral arteries in the first trimester, and the second wave convert the myometrial segment in the second trimester (Lipper E, et al, 1981).

As the result of this physiological change, the diameter of spiral arteries increase from 15- 20 to 300 – 500 mm. Thus reduced impedance of flow and optimizing fetomaternal exchange in the intervillous space.

During early pregnancy trophoblastic cells invade this space and disrupt the wall of the spiral arteries as part of the process of placenta formation.

There are two separate waves of invasion. Between implementation and 10 weeks, the trophoblastic invasion is limited to the decidual layer. From about 14 weeks until 22 weeks, the invasion extends as far as the spiral arteries. This invasion of spiral arteries affects the resistance to blood flow

within the spiral arteries and thereby in the arcuate and main uterine arteries.

Pregnancy requires dramatic changes in the blood flow, for the development of the placenta with the use of Doppler ultrasonography. The mean flow of the blood in the left uterine artery was determined to be about 100 milliliters (mL) per minute; in none pregnant women about 120 mL per minute during early pregnancy and increasing to about 350 mL/ min near term. During this period, the uterine artery increases in diameter from an average of 1.6 mm to 3.7 mm (Barker DJ, et al, 1993).

Hypertension or preeclampsia and intrauterine growth restriction remain cause of maternal and prenatal morbidity and mortality. Maternal complications of hypertension include coagulopathy, renal and liver failure, and stroke.Adults who were affected by intrauterine growth restriction in utero are at increased risk of cardiovascular diseases, hypertension (Phipps K, et al, 1993).

Preeclampsia and intrauterine growth restriction are characterized by abnormal placenta formation (Martyn CN, et al, 1996) which results indicate utero blood flow. This has led to the idea of using Doppler ultrasonography to assess the velocity of uterine artery blood flow as part of routine ultrasound screening (Pijnenborgr, et al, 1980). Lowend – diastolic velocities and an early diastolic notch characterized the wave

form of uterine artery blood flow in women arenot or are in their first trimester.Persistence of diastolic notch beyond 24 weeks gestation, or abnormal flow velocity ration have been associated with inadequate trophoblasthypoxemichypoxia (uteroplacenta insufficiency).

Small – for – gestation age fetus may be constitutionally small, with no increased prenatal death or morbidity or they may be growth – restricted due to either low growth potential. The result of genetic disease or environmental damage or due to reduce placenta perfusion and uteroplacental insufficiency. Analysis of samples obtained by cordocentesis has demonstrated that some small for gestation fetuses are hypoxemic – hypercapnic, hyperlacticemic and academic. (Manning FA, et al, 1993) Furthermore, both respiratory and metabolic academia increase with hypoxemia, in umbilical venous blood, mild hypoxemia may be present in the absence of hypercapnia or academia. In severe uteroplacental insufficiency, the fetus cannot compensate hemodynamically and hypercapnia and academia increases exponentially. The carbon dioxide accumulation is presumably the result of reduced exchange between the uteroplacental and fetal circulation due to reduced blood flow. The association between hypoxemia and hyperlacticemid supports the concept of reduced oxidative metabolism of lactate being the cause ofHyperlacticemid, and, under these circumstances the fetus appears to be not producer of lactate.

Cross- sectional studies in pregnancies with growth restriction, fetus have shown that increase impedance of flow in the uterine and umbrical arteries is associated with fetal hypoxemia and academia (Mills JL, et al, 1984). These data support the finding from histopathological studies that, in some pregnancies with small – far- gestation fetuses there are:

(1) Failure of normal development of maternal development of material placenta arteries into low- resistance vessels and therefore, reduced oxygen and nutrient supply to intervillous space (Uzan S, et al, 1991).

(2) Reduction in the number of placenta terminal capillaries and small muscular arteries in the tertiary stem villi and therefore of eternal – fetal transfer. (Sibai B. M, et al, 1994)

(3) Doppler ultrasound has enabled the non- invasive confirmation of the so- called brain sparing, effect in human fetus.

2-15 Pathological finding in preeclampsia and IUGR:

Preeclampsia and intrauterine growth restriction are associated with an inadequate quality and quantity of the maternal vascular response to placentation. In both condition, there are characteristic pathological finding in the placenta bed.

- Bronses et al, examined placenta bed biopsies from pregnancies complicated by preeclampsia and reported absence of physiological change in the spiral arteries

beyond the decidualmyometriul junction in more than 80% of the cases (Barker DJ, 2004).

- Robertson examined placental bed biopsies from hypertensive women and found a difference between the lesion seen in women with preeclampsia and those with essential hypertension (Doubilet PM, et al, 1995). In preeclampsia there was necrotizing lesion with foam cells in the wall of the basal and spiral arteries, which was referred to as acute atherosis. In essential hypertension, there were hyperplasic lesions in the basal and spiral arteries.

- Sheppard and Bonnar reported that, in pregnancies with intrauterine growth restriction, irrespective whether there is coexistent preeclampsia or not. There are atheromatous-like lession that completely or partially incclude the spiral arteries; these changes are not present in pregnancies with preeclampsia in the absence of IUGR (Hadlock F, 1994).

- In contrast, Brosens etal, reported lack of physiological change in all cases of preeclampsia, irrespective of the birth weight and in most casesof intrauterine growth restriction. However, acute, a therhosis was found only in preeclampsia (Queenan JT, 1994).

- Khonget al- reviewed some of the archived biopsies of Brosens et al (Queenan JT, 1994). They assessed proportion of spiral arteries converted to utero placental arteries in all cases of preeclampsia and in two- third of those with

I.U.G.R (defined as birth weight $< 10^{th}$ centile), there was no evidence of physiological change in the myometrial segments. Furthermore, complete absence of physiological changes throughout the entire length of some spiral arteries was seen in approximately half the cases of pre-eclampsia and (IUGR).

2-16 Uterine artery wave form measurements during pregnancy:

Doppler is a method by which information can be obtained by evaluating the changes in waveform (sound- radar- light) in which the speed and direction of an object (blood- rain- stars) can be determined, in fetal medicine we use the Doppler principle to evaluate changes in sound waves which inform as about the direction and velocity of blood flowing through vessel and the heart using technology and plotting it against time, characteristic of blood flow in the pregnant women and the fetus can be measured.

The uterine artery can be evaluated by direct visualization, i.e examining the characteristics of the waveform to determine if notching is present or absent, or by qualifying the waveform by measuring the blood flow velocity or systole (maximal contraction of the heart) and peak diastole (maximal relaxation of the heart). These values are then computed to drive Ratio. The most common approach is to measure resistance index (Ri)

which the peak of systole is divided by the sum of systole and diastole.

Ri = peak systolic flow (A)-least diastolic flow.

(B) peak systolic flow

Pi = peak systolic flow (A) – least diastolic flow

(B) mean blood flow velocity (Gosling RG, et al, 1974)

2-16-1 Techniques of obtaining waveforms:

- Campbell et al, used pulsed wave Doppler to obtain velocity waveform, arcuate arteries, which were described as vessel in the wall of the uterus distinct from common, internal and external iliac arteries (Campbell S, et al, 1983).

- Trudinger – et al, described the use of continuous wave Doppler to obtain velocity wave forms from branches of the uterine artery in the placenta bed (Turdinger BJ, et al, 1955). The placenta site was located using real time ultrasound and the Doppler probe was then pointed at the center of the placenta bed and searched until characteristic wave forms were obtained. Validation of the method was performed by directing a pulse wave Doppler facility along the same line and obtaining identical wave forms from sub placental vessels. Schulman et al, described the use of continuous wave Doppler ultrasound.

The Doppler probe was directed into the Para uterine area in the region of the lower uterine segment and rotated a characteristic waveform pattern was recognized in the early

stages of the study. The methodology was validated with duplex equipment or by in vivo measurements obtained during cesarean section. They found that pattern of uterine, arcuate and iliac vessels could be differentiated from each other vessel in the pelvis.

The presence of an early diastolic notch was noted and found to disappear between 20- 26 weeks.

Figure (2.2): Insonation of the uterine artery at the cross over with iliac artery.
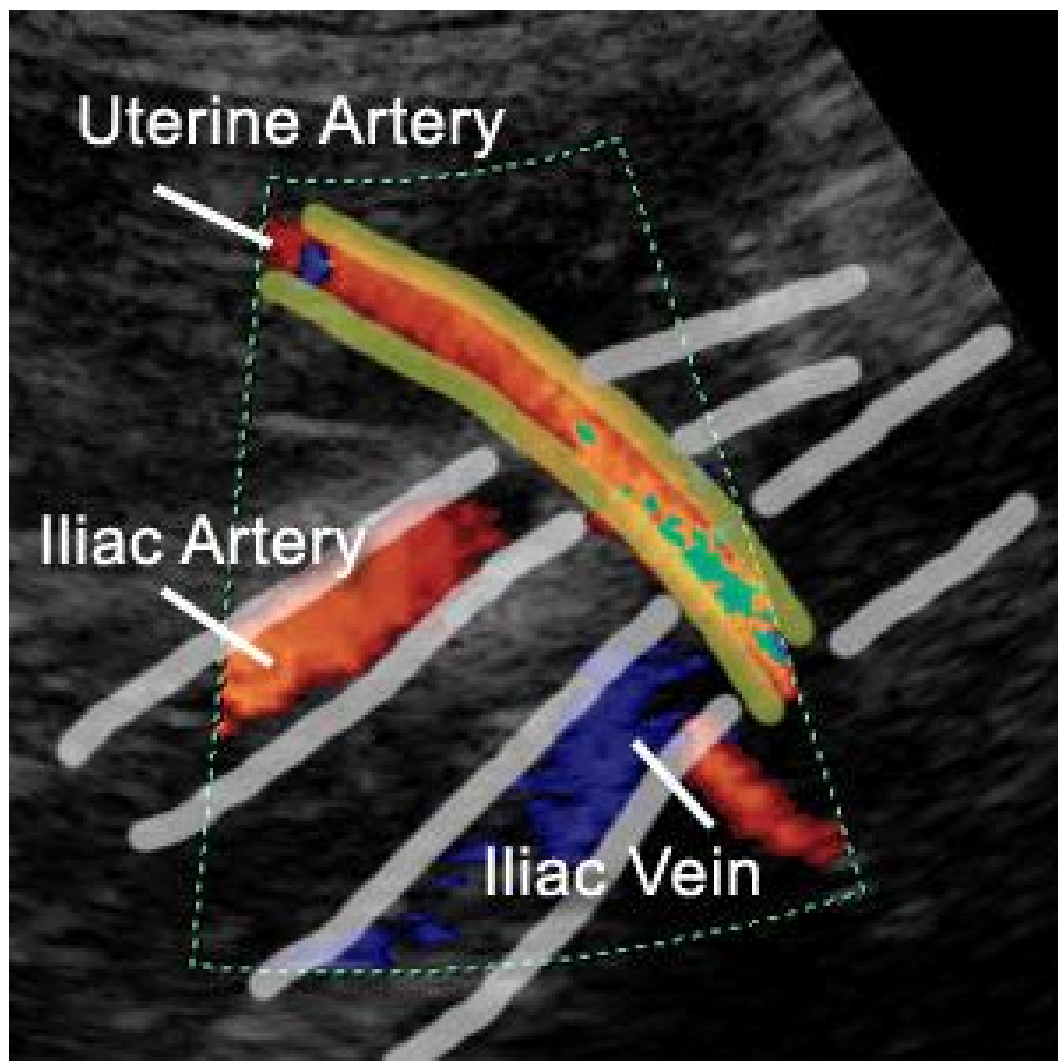
Figure (2.3): Normal uterine artery wave form
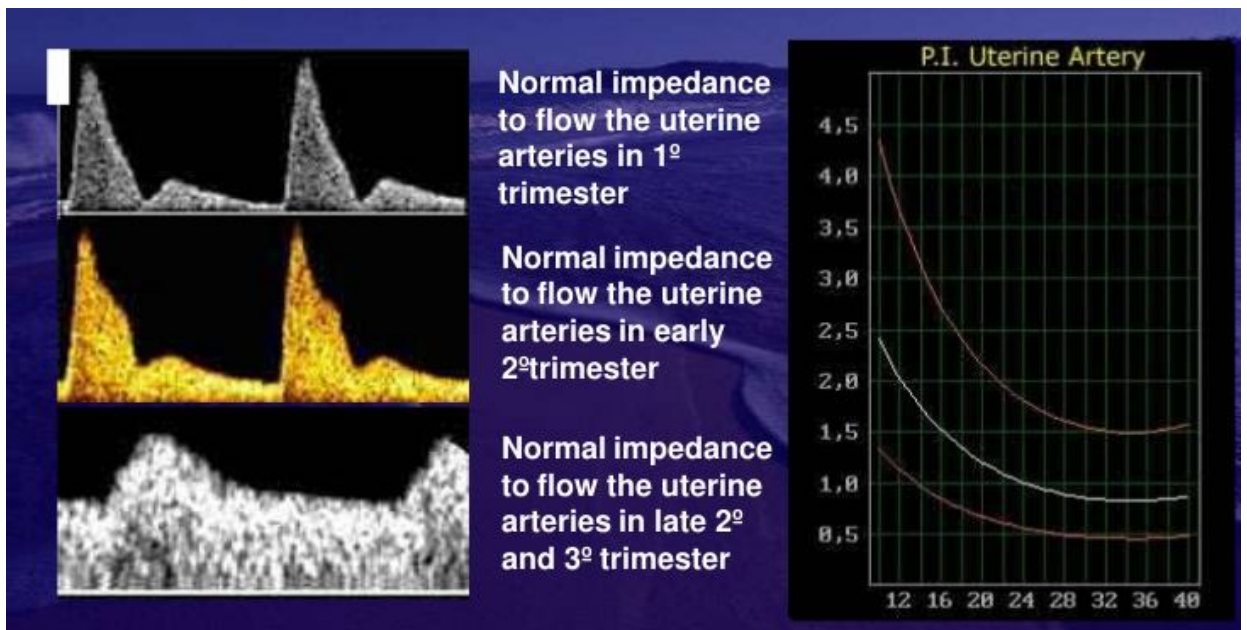
Doppler indices:

Explanation of Doppler indices:

A/C ratio:

- Ratio of peak systolic to early diastolic velocity

Bilateral notching:

- Presence of early diastolic notching in waveforms of main arteries.

D/S ratio:

- Ratio of diastolic to systolic velocity.

Pulsatility index:

- Peak systolic flow minus end diastolic flow divided by mean flow (A-B)/ m

Resistive index and notching:

- Resistance index combined with unilateral or bilateral early diastolic notch.

Resistive index or notching:

- Resistance index with or without unilateral or bilateral diastolic notching.

S/D:

- Ratio of peak systolic to late diastolic velocity also known as A/B ratio.

S/D or notching:

- S/D ration with or without unilateral or bilateral early diastolic notching.

Unilateral notch:

- Presence of early diastolic notching waveform of one main uterine artery.

Figure (2.4): Flow velocity indices

S = systolic peak (max. velocity)
D = end diastolic flow
Vm = mean velocity
A = Temporal average frequency over 1 cardiac cycle

Doppler Indices
RI = (S - D) / S (Pourcelot, 1974)
PI = (S - D) / A (Gosling, 1976)
S/D Ratio = S/D (Stuart & Drumm, 1980)
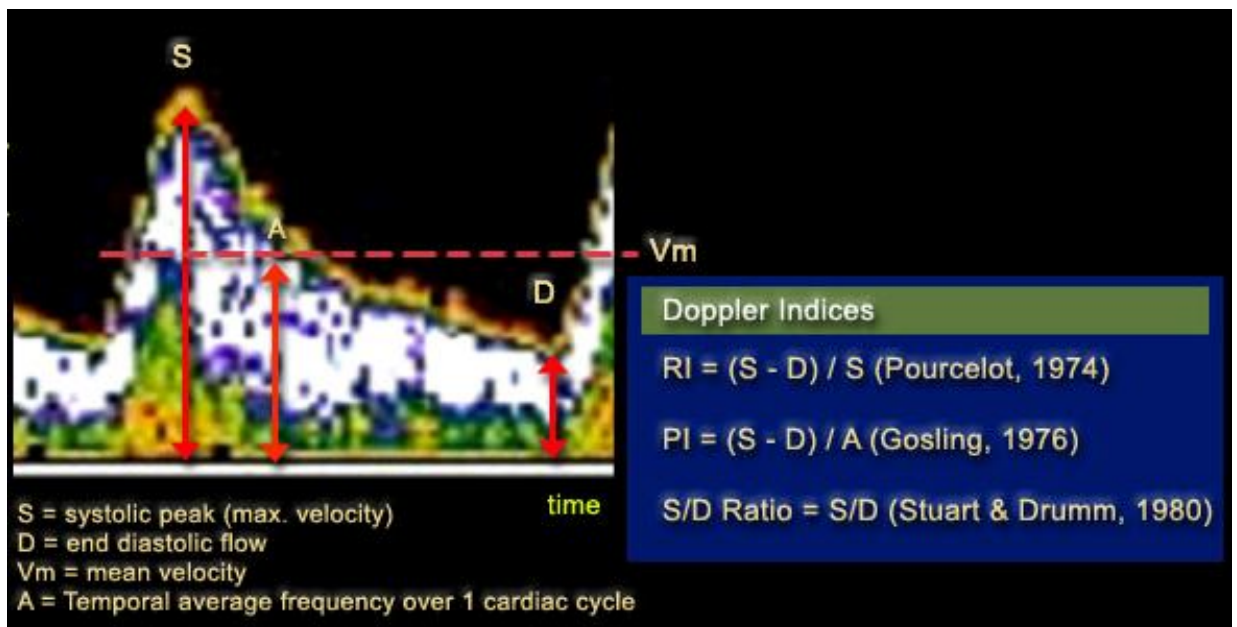
Doppler indices:

$R_1 = (S - D) / S$ \qquad (Pourcelot, 1974)

$P_1 = (S - D) / A$ \qquad (Cosling, 1976)

S / D Ratio = S / D (Stuart & Druman, 1980)

S = systolic peak (max velocity)

D = end diastolic flow

V_m= mean velocity

A temporal average frequency over 1 cardiac cycle:

The relative merits of indices used 1 uterine arteries have discussed elsewhere (Gosling RG, et al, 1974) commonly used indices available on most commercial scanners are:

1- Resistance index (R_i) also called resistance index or Pourcelot's index.

2- Systolic/ diastolic (S/D) ratio, sometime called the A/B

3- Pulsatility index.

These indices are based on the maximum Doppler shift waveform and their calculation is described in figure D.

The Ditakes slightly longer to calculate than the R_i or S/ D ratio because of the need to measure the mean height of the wave form. It does, however give a broader range of waveform shapes when there is no end- diastolic flow in addition to those indices the flow waveform may be described or categorized by the presence or absence of particular feature for example the absence of end diastolic flow and the presence of post- systolic notch.

Generally, a low pulsatility waveform is indication of low distal resistance and high pulsatility waveform occur in high resistance vascular beds, although the presence of proximal

stenosis vascular steal or arteriovenous fistulas can modify waveform shape. Should be taken when trying to interpret indices as absolute measurement or either upstream or downstream factors for example, alteration in heart ratio- can alter the flow waveform shape and use significant change in the value of indices.

2-16- 2 Abnormalities in Doppler waveform:

To understand the changes in uterine artery waveform. It is to compare the non- pregnant and pregnant state because of high resistance to blood flow in the none- pregnant uterus to waveform demonstrates nothing at the beginning of diastole with low to flow at the end of the diastole, once pregnancy occurs puzzles in the placenta develops, resulting in low resistance of blood flow with communication increase in the height of the diastolic waveform. The following ultra sound images demonstrate rate blood flow in the uterine arteries in a non- pregnant patient.

Figure (2.5): Non pregnant uterine artery wave form
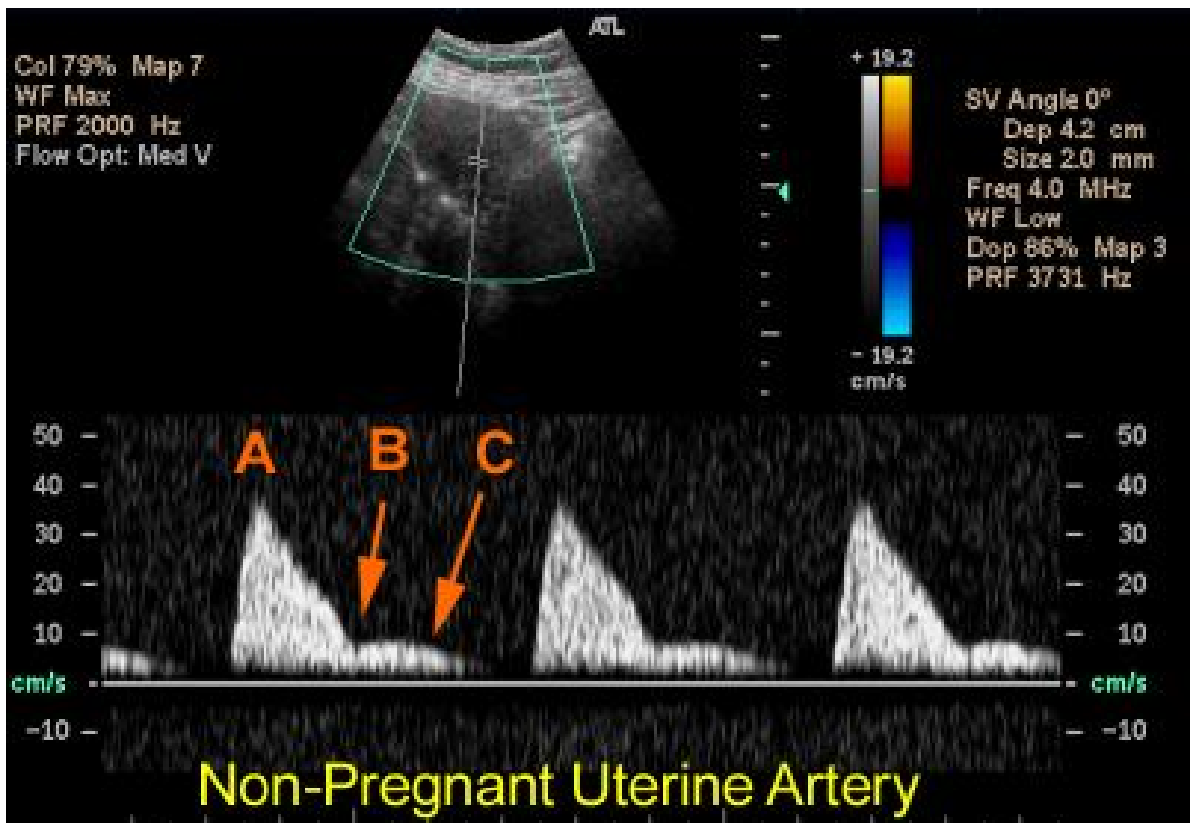
Notching with a normal resistance index
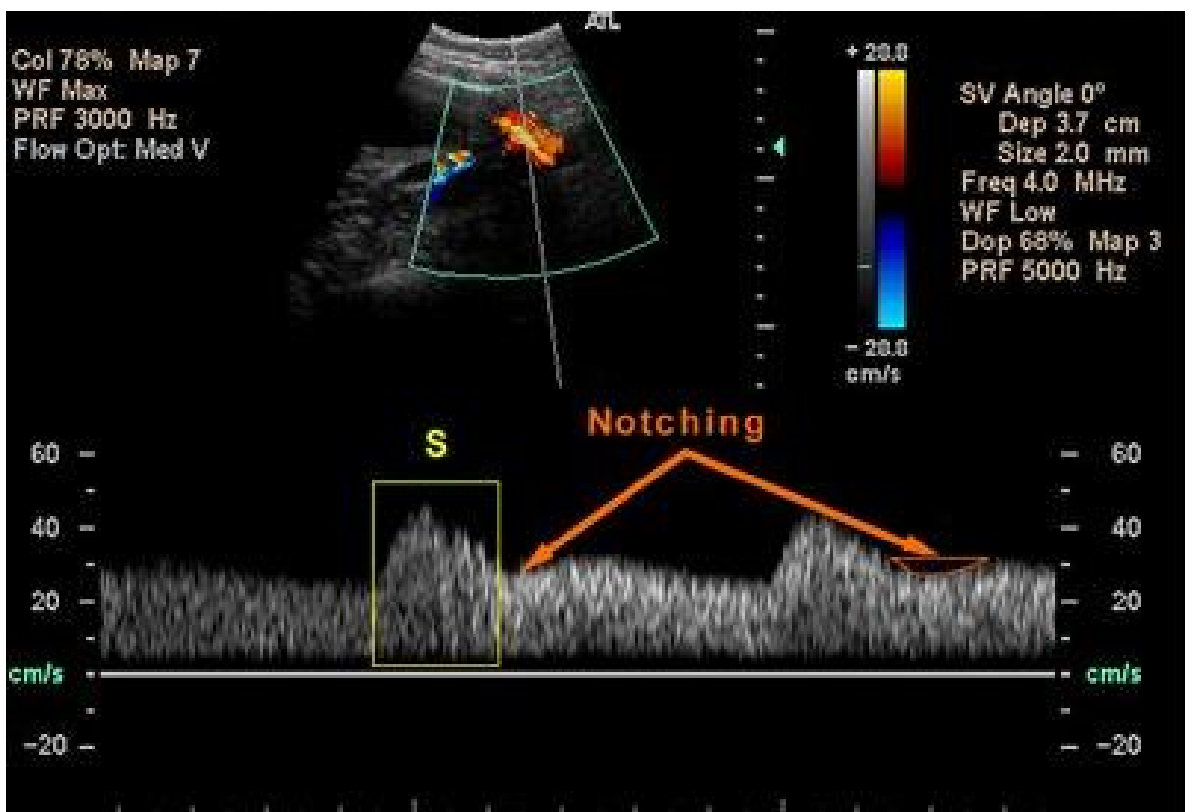
Type 1 abnormal resistance index:

Once the waveforms are obtained measured, the results are plotted on graph to determine if the blood flow during diastole is normal or abnormal resistance index increase to a value above the upper range of normal. This identifies fetus at risk or who may undergone (too small) to determine the resistance index the peak of systole is divided by the sum of the systole and diastole measurement. A value is greater than 0.58 is considered to be abnormal one of the problem with this measurement is a higher false- positive ratio than if the presence or absence of notching (see below) for this reason. They prefer using the presence or absence of "notch" to determine if the waveform normal or abnormal.

Figure (2.6): Up normal development of the uterine artery

ABNORMAL UTERINE A. DOPPLER
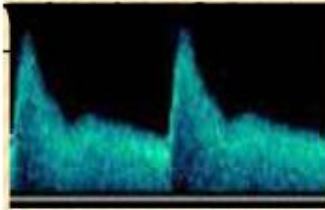
Normal impedance to flow in the uterine arteries (with the characteristic waveform of early diastolic notching)
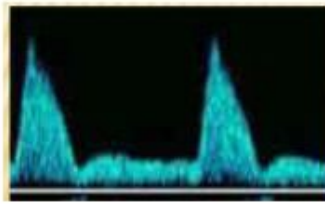
Increased impedance to flow in the uterine arteries (with the characteristic waveform of early diastolic notching)
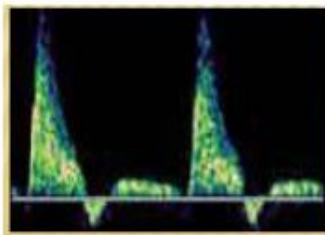
Very high resistance to flow in the uterine arteries (with reverse diastolic flow)
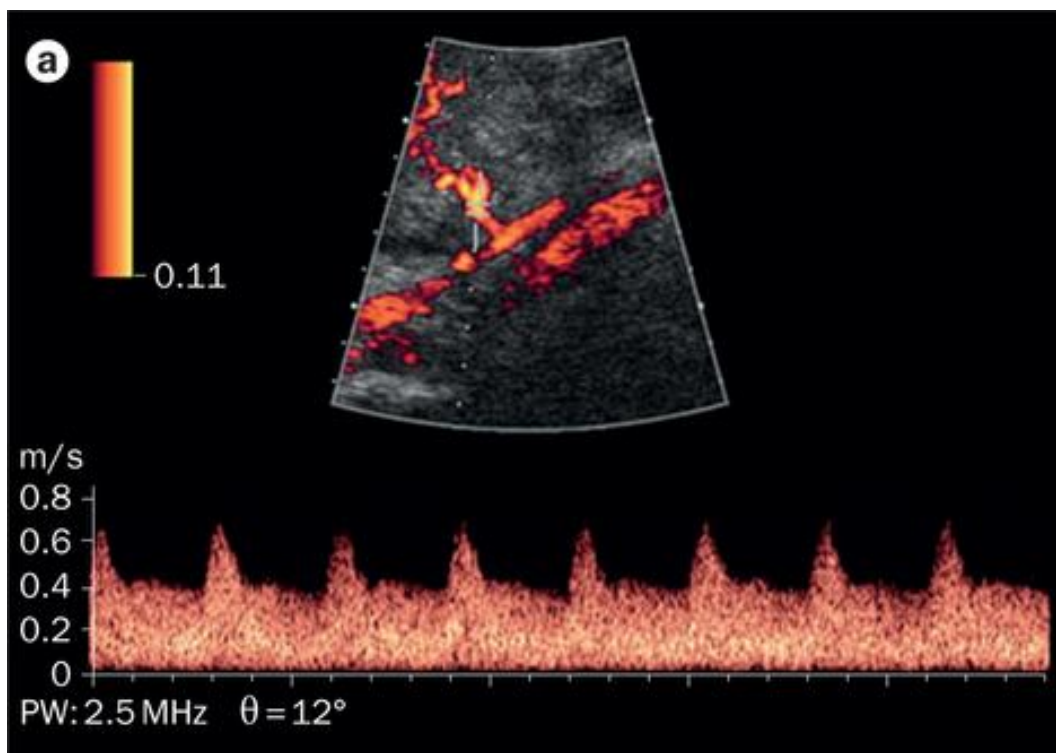
Figure (2.7): Increase resistance index:
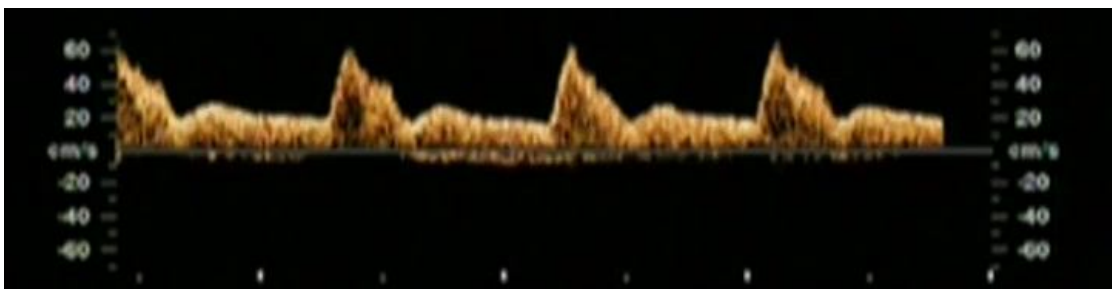
The resistance index is measured to determine if it is abnormally high. In this example the low diastolic flows result in an abnormal resistance index.

Type II: Mild notching of the uterine artery:

This is more serious farm than type I, because there is "notch" at the beginning of the diastole. The notch is the result of an increase resistance to blood flowing into placenta. The reason for this is because the vessel in the placenta are not enlarging or dilating as they should when this occurs notching is present in the Doppler waveform. However, as in this example blood flow at the end of diastole appears to be normal, thus giving a normal resistance index the presence of a notch, even with a normal resistance index places the patient at high risk for adverse fetal outcome.

This illustrates notching with normal resistance index. The presence of notch places the patient in high risk for adverse pregnancy outcome.

Fig (2.9): Notching with normal resistance index

Type III: Severe notching with abnormal resistance index:

When the resistance index is abnormal (low- diastolic flow) and a notch is present. This places the patient at the highest risk for adverse pregnancy outcome.

Figure (2.10): Illustrates notching with abnormal resistance index
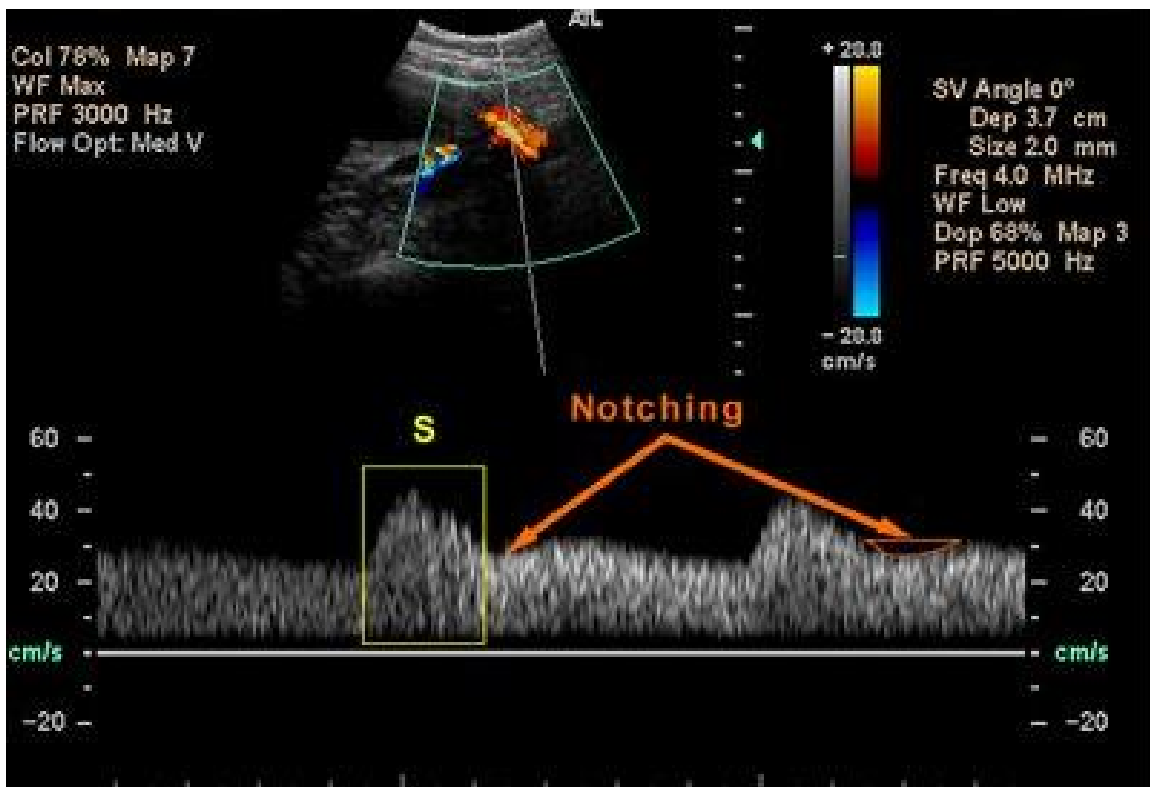
This illustrates that notching with an abnormal resistance index.

The combination of those two findings places the patient at increased risk for adverse pregnancy outcome.

2-17 The benefits of uterine artery surveillance:

Recent studies have found that surveillance of high risk fetus with abnormal uterine blood flow may decrease morbidity and mortality. The majority of the earlier studies examined the uterine artery during the second trimester of pregnancy (20- 24

weeks). However, recent studies have suggested that identification of abnormal Doppler waveform during the first trimester and subsequent treatment with low dose of spirin may be more beneficial than waiting until the second trimester to evaluate these vessels. A series of screening studies involving assessment of impedance to flow in the uterine arteries have examined the value of Doppler in identifying pregnancy at risk of complications of impaired placentation.

2.18 Studies in selected population:

Arduini et al. examined two women who had essential hypertension or renal disease or a previous pregnancy complicated by pregnancy - induced hypertension (Eclampsia trail collaborative group, 1995). They measured impedance to flow in the arcuate arteries at 18- 20 weeks of gestation and defined as an abnormal result a resistance index of more than 0.57 they reported that this test identified 64% of pregnancies that subsequently developed pregnancy induced hypertension.

In a similar study. Jacobson et. examined 91 women who had chronic hypertension, history of preeclampsia of fetal loss and a variety of other medical condition (Jacobson S, et al, 1990). They measured impedance to flow in the arculate arteries at 24 weeks of gestation and defined as an abnormal result a resistance of more than 0.57, Doppler signal could not be obtained in 8% of women and these pregnancies were considered to have abnormal test result the sensitivity of the test

for pregnancy induced hypertension was 44%. This study also examined prediction of intrauterine growth restriction (birth weight below 10[th]centile for gestation) which was found in 18% of the cases.

- Zimmerman et. al., examined 172 women at high risk for hypertensive disorders of pregnancy or intrauterine growth restriction (Zimmermann P, et al, 1997). They measured impedance to flow in the uterine arteries at 21 – 24 weeks of gestation and defined an abnormal result by a resistance index of more than 0.68. The main problems with abnormal uterine artery blood flow that persist throughout pregnancy, is that there is an increased risk of preeclampsia, high blood pressure, and protein in the urine) during the late second and third trimester of pregnancy when this occurs the only treatment is delivery. In addition fetus for mother who have an abnormal uterine artery, Doppler waveform have an above the 90[th]centile and the presence diastolic notches in both uterine arteries was found in 4.2% of cases.

- Irion et al, examined the uterine artery in 1159 nulliparous women at 26 weeks (Campbell S, et al, 1986).Preeclampsia, intrauterine growth restriction and preterm delivery occurred in 4%, 11% and 7% of the pregnancies, respectively. At 26 weeks increased impedance to flow (resistance index greater than 0.57) was present in 13% of cases and the sensitivity of

the test was 26% for preeclampsia, 29% for growth restriction and 15% for preterm delivery.

- Kurdi et al, examined the uterine artery by color Doppler in 946 unselected women at 19 – 21 weeks of gestation (Hanretty KP, et al, 1989). In 12.4% of cases there were bilateral notches and in this group, the odd ratio for developing preeclampsia was 12.8, and for preeclampsia requiring delivery before 37 weeks. It was 52.6 when the uterine artery Doppler studies were normal, the odd ratio for developing preeclampsiawas 0.11 and for intrauterine growth restriction (birth weight below 5th centile for gestation), it was 0.3 in women with bilateral notches and a mean resistance index greater than 0.55 the sensitivity for preeclampsia and fetal growth restriction were 62% and 37% respectively and for these complications requiring delivery before 37 weeks.

It was concluded that women with normal uterine artery Doppler studies at 20 weeks constitute a group that have a low risk of developing obstetriccomplications related to utero placenta insufficiently, whereas women bilateral not have an increased risk of the subsequent development of such complications, in particular those requiring delivery before term consequently, the result of Doppler studies of the uterine arteries at the time of the routine 20 week anomaly scan may be of use

in determining the type and level of maternal care that is offered to women.

- Bewley et al. calculated the average resistive index from the left and right uterine and arcute arteries in 925 pregnancies at 16- 24 weeks gestation (Bewley S, et al, 1991) when the resistive index was greater than 95th centile, there was 10-fold increase in risk for severe adverse outcome define by fetal death, placenta abortion, intrauterine growth restriction or preeclampsia.

- Bower, et.al. examined the uterine artery in 2058 pregnancies at 18- 22 weeks (Bower S, et al, 1993) on abnormal result, defined by a resistive index above the 95th centile or the presence of an early diastolic notch in either of the two uterine arteries was found in 16% of the pregnancies.

This study highlighted the fact that abnormal Doppler result provides a better prediction of more severe types of pregnancy complication.

- Valensise et al examined the uterine arteries in 272 primary gravitas at 22 weeks of gestation (Valensise H, et al, 1993), an abnormal result, define by increased impedance (mean index more than 0.58) was found in 9.6% of patient.

- Narther et al, examined the uterine arteries at 19- 24 weeks of gestation in 45 nulliparous women and they found increased impedance (resistance index greater than 0.57 on placental side) in 11% of case (North RA, et al, 1994).

Methodology

The aim of this study was to identify the abnormal uterine Doppler waveform during 12 – 24 weeks of gestation in high risk patient who had history of preeclampsia or hypertensive or intrauterine growth restriction or prenatal death in their previous studies.

3.1 materials

3.1.1 Data collection tools:

Screen of uterine artery Doppler in high risk patient between 12- 24 weeks of gestation will be done in obstetric and gynecology department in Turkish Hospital outpatient clinic. The gestational age was calculated with the use of color Doppler – Toshiba ultrasound machine Nemioxgssa- 580A. It is afull digital compact class diagnostic ultrasound system by Toshiba manufacture using of 3.5 (MHz) convex probe and ultrasound gel. With real time Doppler study of uterine artery while crossing iliac artery, uterine artery blood flow was assess with identification of diastolic notch, three to five consecutive wave forms from uterine artery were obtained and the image frozen. The resistant index and the pulsatility index were calculated .

3.2 Methods and techniques of data collection:

During Doppler study mother lie in semi recumbent with slight lateral tilt. This minimizes the risk of developing hypertension syndrome.

3.2.1 Study design:

This study was carried out in Turkish Hospital in Alkalakla. The hospital provides health services of all branches of medicine. It has obstetrics and gynecology department includes inpatient and outpatient units. The total number of patients seen in outpatient clinic > 50 females daily.

3.2.2 Study population:

Women at 12 – 24 weeks of gestation, with history of pregnancy induced hypertension or intrauterine growth restriction or unexplained prenatal fetal death in their previous studies.

3.2.3 Sampling:

Non probability convine sample, all high risk women with singleton pregnancy between 12- 24 weeks of gestation attending obstetrics and gynecology department outpatient clinic in the period of Nov. 2014 – Jun. 2015. This was found to be 50 females.

3.2.4 Inclusion criteria

All high risk women with single pregnancy between 12 – 24 week of gestation presented at ultrasound department in Turkish hospital during the period of the study.

3.2.5 Exclusion criteria

- Any case with multiple pregnancies.
- Any case with PIH in the current pregnancy.
- Any high risk patient out of the previous risk factor.

3.2.6 Data collection

Data was collected by direct interview of the pregnant women prospectively by the on duty registrar using age parity gestational age, previous history of PIH, IUGR and prenatal death. Trans abdominal probe uterine artery wave form was identified pulsed wave Doppler applied uterine artery blood flow and different Doppler indices RI and PI were measured.

3.2.7 Data analysis

Data was collected and master sheet was prepared. The data was analysed using statistical package of social science (SPSS) software program, significant testing of differences between proportions was conducted using chi-square and T- tests for independent values, were applicable. The results were present in tables and graphs designed using Microsoft excel program.

3.2.9 Ethical consideration:

Written consent was taken from the purpose of the research prior to the commencement of the study.

Results

4.1 During the period from Nov. 2014 till Jun. 2015, there were a total of 50 women examined for routine ultrasound scan with uterine artery Doppler screening.

- Table 1 and figure 1 shows the distribution of parity among the study population low parity women (para 0, 1,2) counted 29 (58%) out of 50 women, multiparas (3-5) counted 19 (38%) while grand- multi para (>5) were 2 (4%). The study showed the highest percentage were (58%) the low parity women. This is due the fact of recurrent miscarriages and good family planning program specially among high risk patients.

Table (4.1): The distribution of the study population according to the parity.

Parity	Frequency	Percentage %
0	3	6
1	11	22
2	15	30
3	9	18
4	6	12
5	4	8
6	1	2
7	1	2
total	50	100
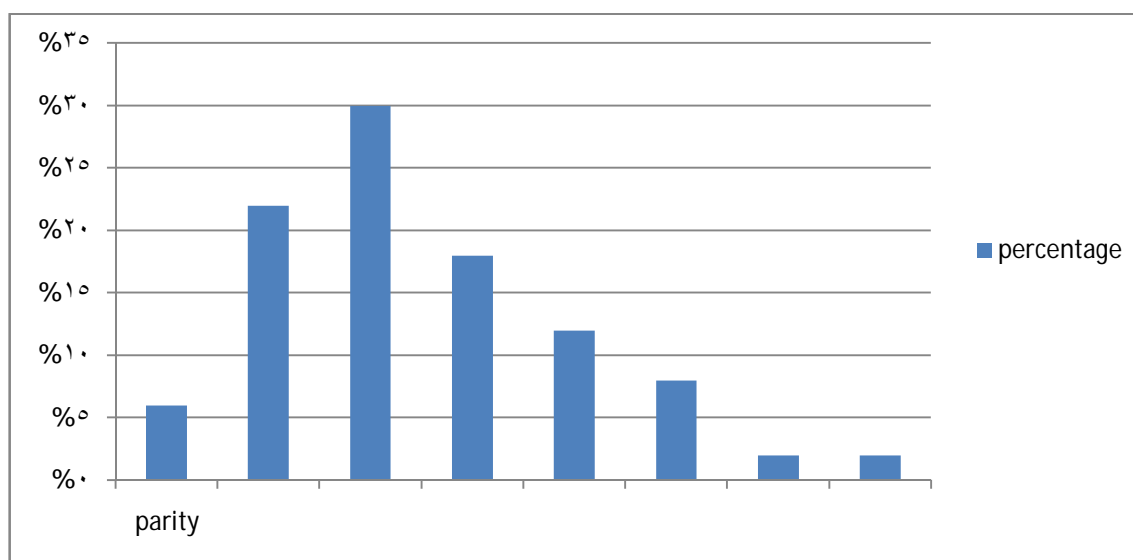
Figure (4.1): The percentage of the study population according the parity

Table (4.2): The distribution of different age groups in years in the study population.

Age group	Frequency	Percentage %
17-11	3	6
22-26	8	16
27-31	9	18
32-36	14	28
37-41	9	18
42-46	7	14
total	50	100
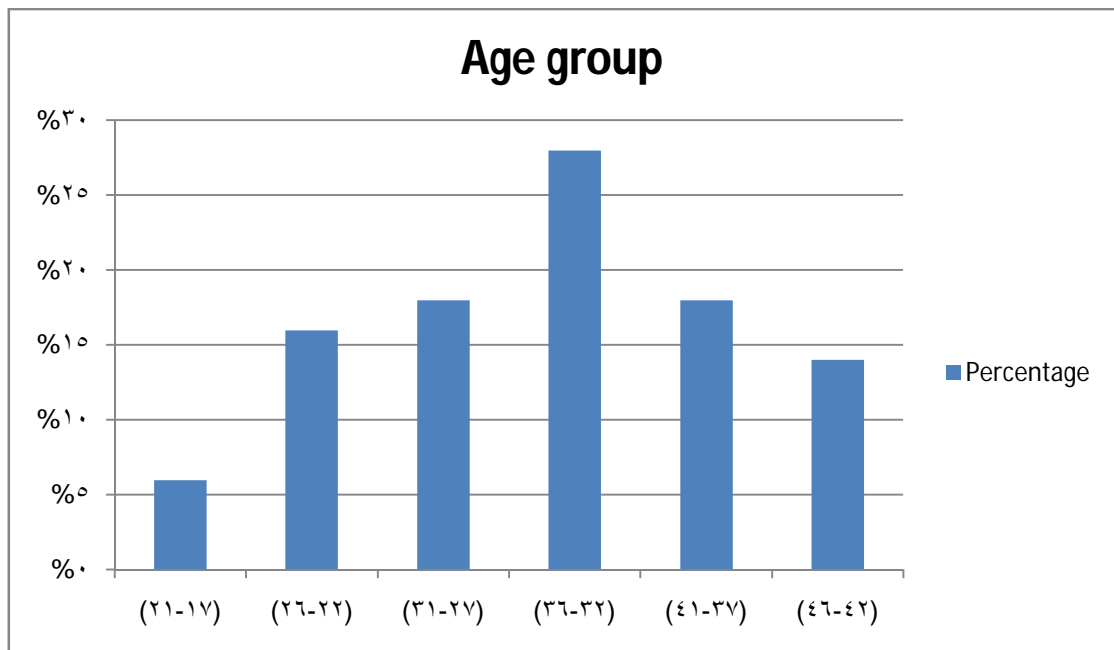
Figure (4.2): The percentage of the study population according to the age

Table (4.4): The distribution of the gestational age in the study population

Gestational age	Frequency	Percentage %
< 13 weeks	6	12
>13 weeks	44	88
total	50	100
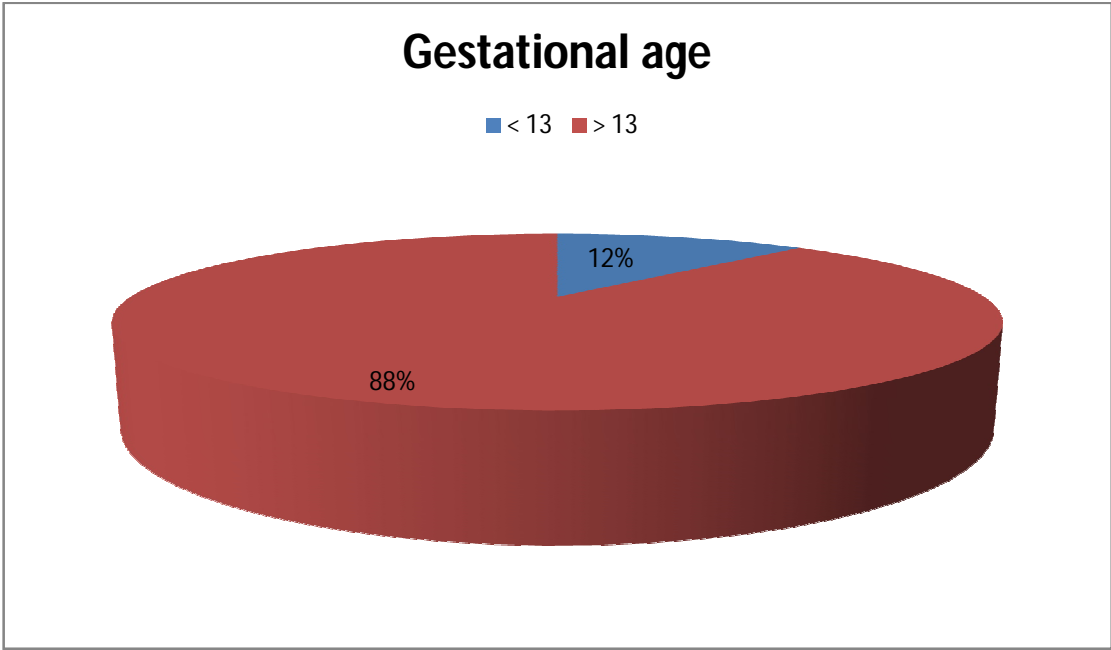
Figure (4.3): The percentage of the gestational age in the study population divided to first and second trimester

Table (4.4): The distribution of the risk factor in the study population

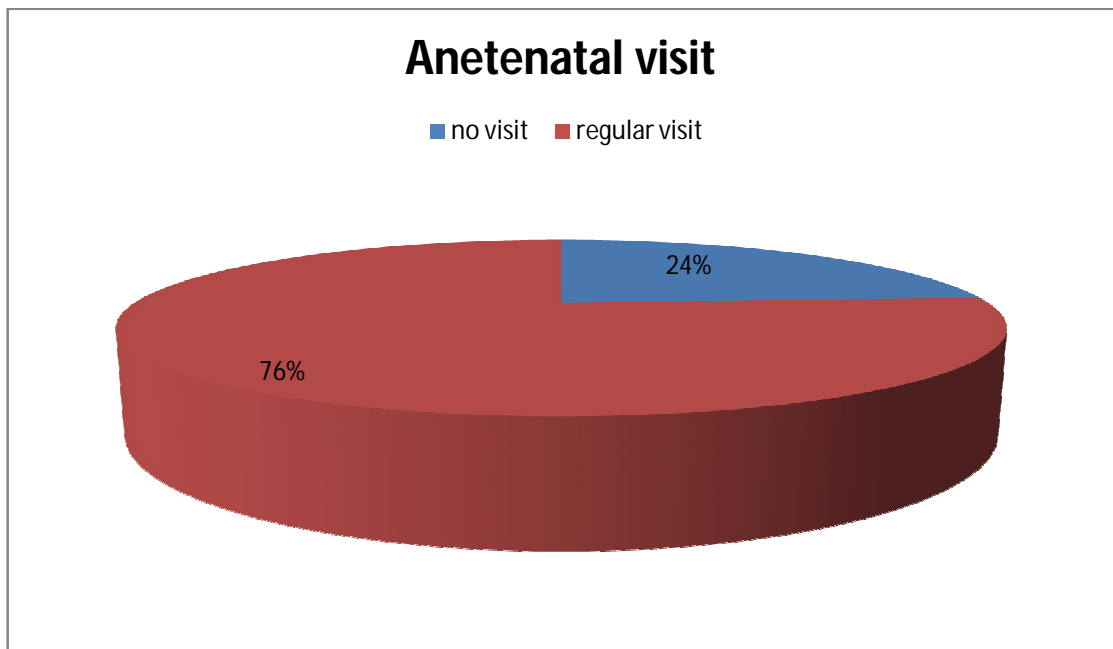| Risk factor	Frequency	Percentage %
PIH	26	52
IUGR	8	16
PND	7	14
PIH + IUGR	3	6
PIH + fits	6	12
total	50	100
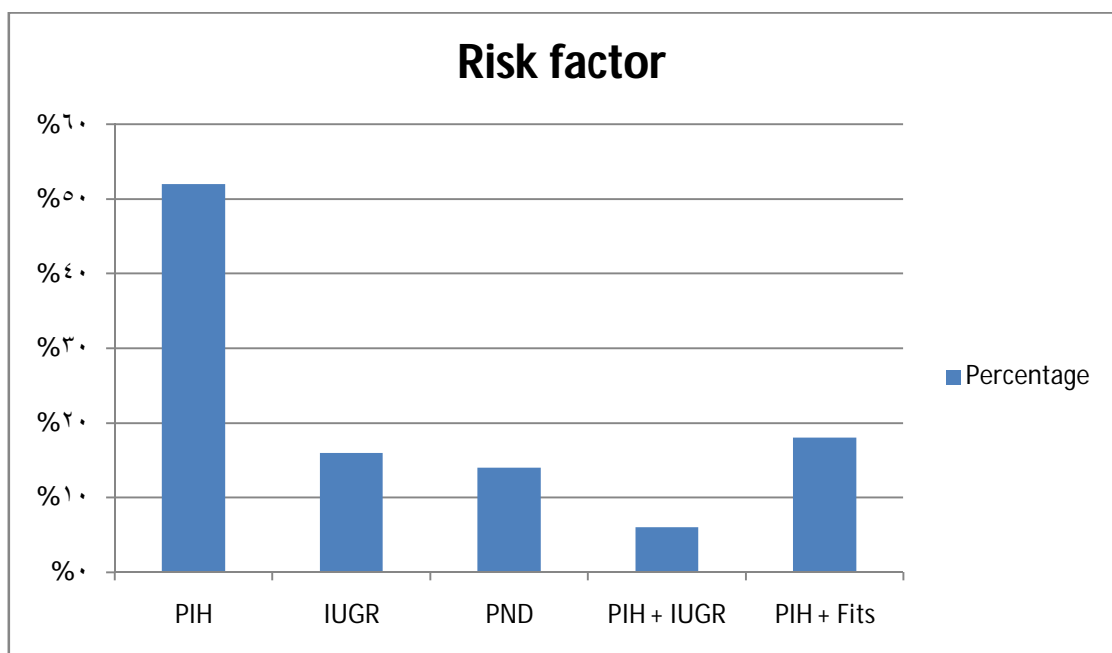
Figure (4.4): The percentage of study population according to the risk factor

Table (4.5): The distribution of blood flow in the study population

Blood flow	Frequency	Percentage %
Normal	41	82
Low	9	18
total	50	100

Blood flow

■ normal ■ low

18%

82%
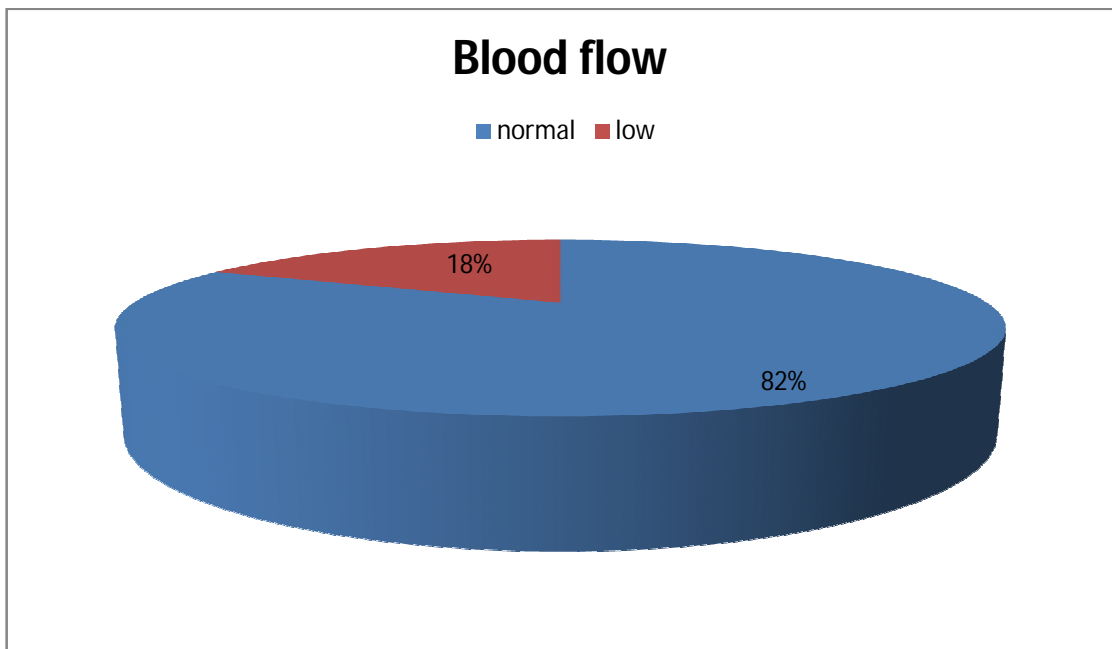
Figure (4.5): The percentage of the blood flow in the study population

Table (4.6): The distribution of diastolic notch in the study population

Diastolic notch	Frequency	Percentage %
Present	47	94
Absent	3	6
total	50	100
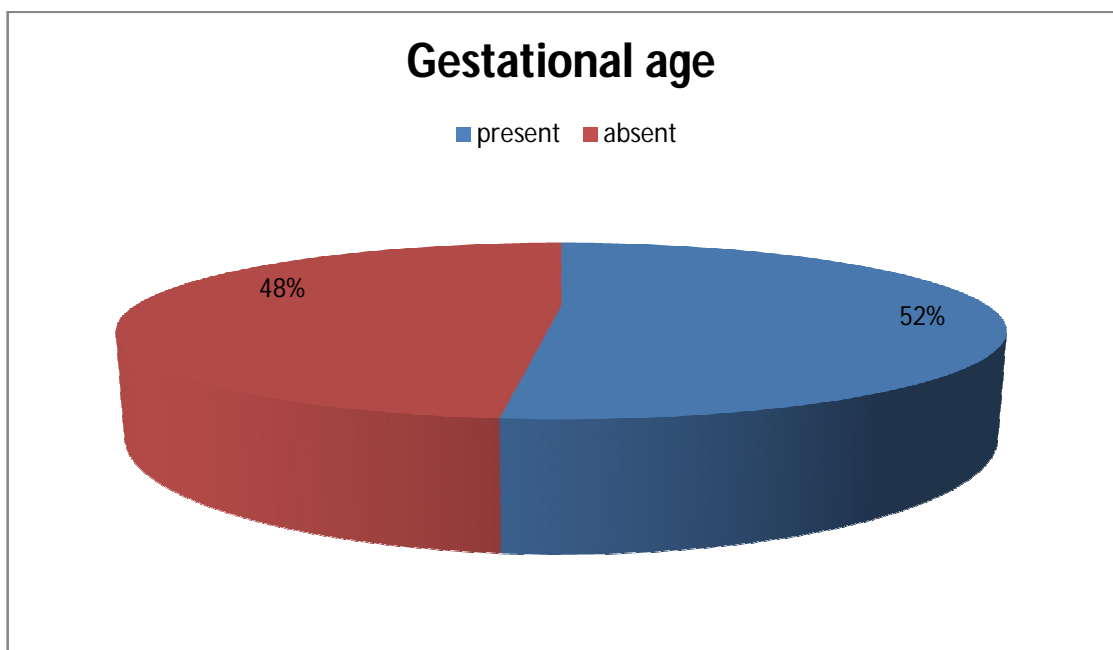
Figure (4.6): The percentage of the diastolic notch in our the study population

Table (4.7): The distribution of antenatal visit in study population

Antenatal visit	Frequency	Percentage %
No visit	12	24
Regular visit	38	76
total	50	100

Figure (4.7): The percentage of the study population according to antenatal visit

Table (4.8): The distribution of occupation in the study population

Occupation	Frequency	Percentage %
House wives	29	28
Working	15	30
Student	6	12
total	50	100
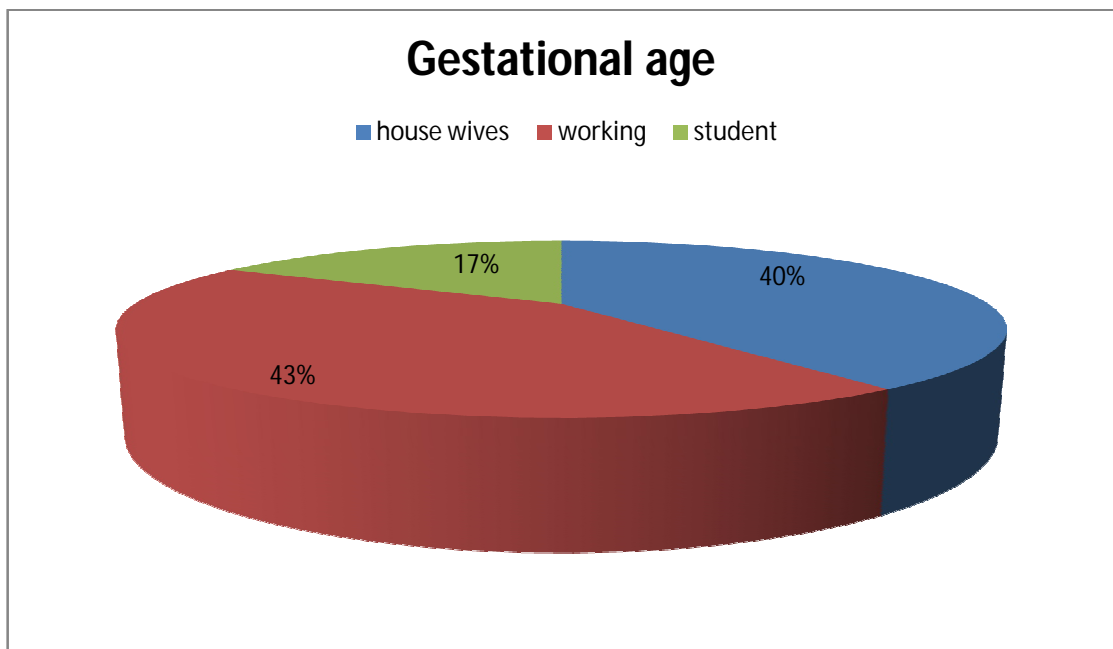
Figure (4.8): The percentage of the study population according to the occupation

5.1 Discussion:

The objective of this study is to evaluate the clinical usefulness of Doppler analysis of uterine artery wave form in pregnancies induced hypertension to assess prediction of IUGR, eclampsia and preeclampsia and it is associated complications and prenatal death.

The study involves 50 women with single pregnancy between 12 – 24 weeks of gestation and all of them considered to be high risk of developing hypertension, IUGR and preeclampsia and it's complications according to their obstetrical history all data from the study based on present or absence of diastolic notch alone/ or with increase resistivity and pulsitility index and previous history of patient risk factor.

The study showed no significant relation between parity and different types of risk factor. This is by using T-test for independent sample. This result due to the proportion of women in the study sample were 29 (58)% out of 50 women all of them were low parity and the complications with pregnancy is usually associated with the high parity.

The study shows the risk factor does not depend on patient age, this by using the T- test for independent sample using risk factor as grouping variable against patient age as test. The majority of age group in our study were 14 (28%) between 32 –

36 years old. This proves that hypertension of pregnancies can happen at any age and parity in hypertensive pregnancies.

The study evaluate the relation of gestational age with uterine artery velocity wave form pattern; hence uterine artery Doppler performed before 16 weeks of gestation is unlikely to be useful screening test due to the physiological trophoblastic invasion of the uterine spiral artery occur at 4 – 16 weeks of gestation so it is better to perform or stop screening test for the uterine artery Doppler between 16- 24 weeks than for the first trimester.

As noticed in the study, most of the cases had normal blood flow (82%) most of them and their first trimester when blood flow was compared with the gestational age, P- value was 0.039 by using T- test for independent value and this suggested that changes in the blood velocity does not occur early in the first trimester of pregnancy especially in mild form of hypertension or mild form of preeclampsia. The remaining who had low blood flow was in their second trimester and they have history of pregnancies induced hypertension when the PIH as the highest risk factor. In the study compare with blood flow, the result shows significant relation between low flow and PIH , P-value was 0.007 by using Chi- square test for independent value.

In this study, the high proportion of women had presence of notch 47 (94%) out of 50 women. This indicates that diastolic

notch was normal Doppler finding in first trimester and second trimester the P- value was 0.001 by using chi- square test.

When compare the patient with the risk factor in this study, result shows that the RI increased in the patient who had history of PIH and fits while PI was increase in the patient who had history of PIH and IUGR. This proves that Doppler indices had good predictive value among severe or chronic hypertension, preeclampsia and IUGR than in the mild cases.

When we compare RI and PI with the gestational age and risk factors this study shows no significant relation, this by using T- test for independent value. This is due to small data sample as compare with the number of the sample mention in the previous studies. Finally, the results suggest that an abnormal flow value form ratio alone or with diastolic notch as measurements parameter used for uterine artery Doppler flow velocity has limited prediction value. For hypertension disease (preeclampsia, IUGR and prenatal death) specially to the risk factor. According to the risk factor the (R1) and (P1) was significantly high in patients with history of severe or chronic (PIH).

The previous studies reported the same result (Tang L. C. et al, Cynthia J. et al, Buchbinder A, et al, Pijnenborgr, et al, Khong TY, et al, Gosling RG, et al).

5.2 Conclusion

Although the study did not establish whether the all step of uterine artery screen in the first and second trimester has good predictive value of PIH and its complication.

The Doppler ultrasound provides a direct method and useful tool in the study of normal uterine blood flow dynamic study must interpreted with caution because sample number were limited, the result of Doppler studies of the uterine artery and the time of routine 20 weeks a normally scan may be of use in determining the type and level of antenatal care that is offered to women. Uterine artery Doppler testing in clinical practice is noninvasive and technical easy and had additional cost when integrated into ultrasound evaluation for high cases. Surveillance of high risk mothers and fetuses with abnormal uterine blood flow may decreases morbidity and mortality rate, the study showed that the significance of notching at 22- 24 weeks high risk factor.

Maternal history had low sensitivity in the detection of early honest form in case of PIH (preeclampsia – IUGR) early and late honest of PIH or preeclampsia, suggested different pathogenesis women with normal uterine artery Doppler studies.

Finally, our finding in this study do not support the role of uterine artery Doppler study in prediction of IUGR, umbilical artery Doppler is the best screen in this.

5.3 Recommendations

- Doppler assessment is none invasive test and thus acceptable to patient and it should be used as routine screening test in the clinical practice to improve the outcome.

- Early screening of the uterine artery wave form should be performed to all high risk patients. This may help in early diagnosis of PIH and its complication and decrease the maternal morbidity and mortality rate.

- Uterine artery blood flow with other Doppler indices could be fairly performed at the time of detailed anomaly scan between 18- 22 weeks of pregnancy for all high risk patients.

- Uterine artery Doppler is very important to fellow up normal pregnancies and also to fellow up PIH to reduce the risk of the pregnancies.
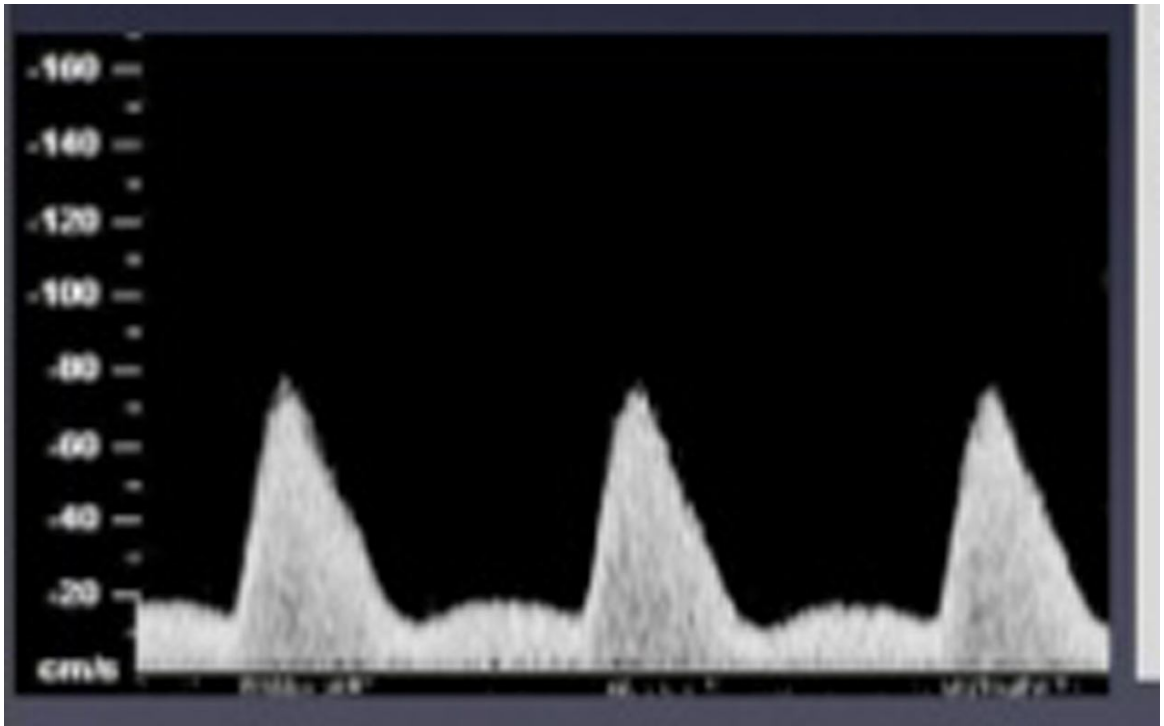
Image (1): 13 weeks with normal blood flow
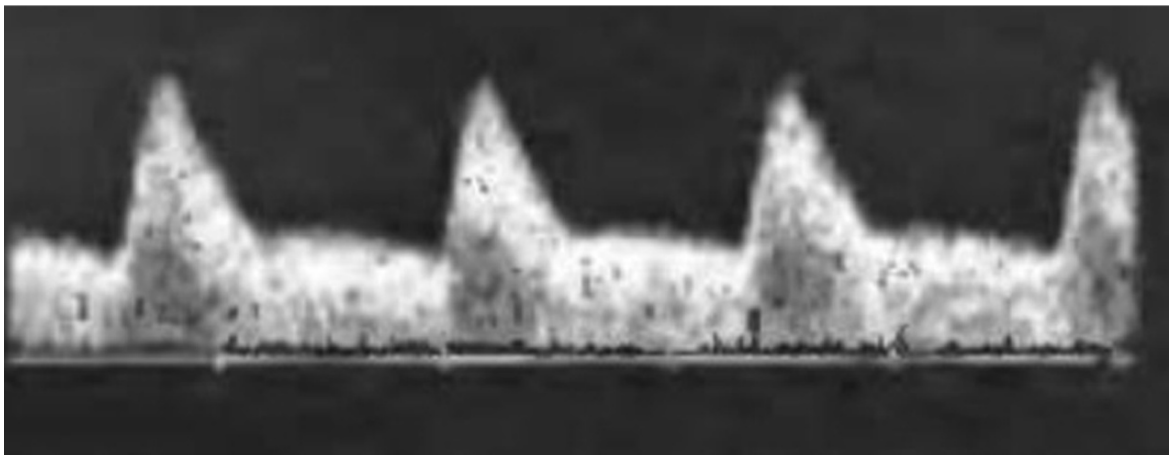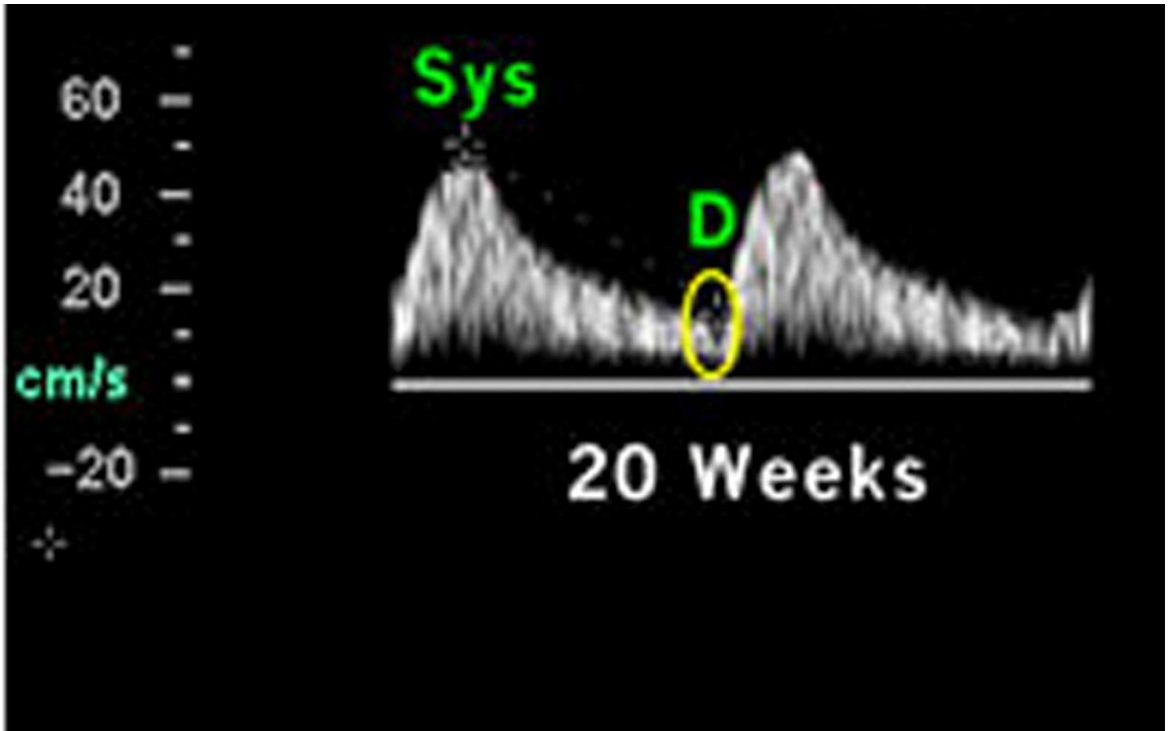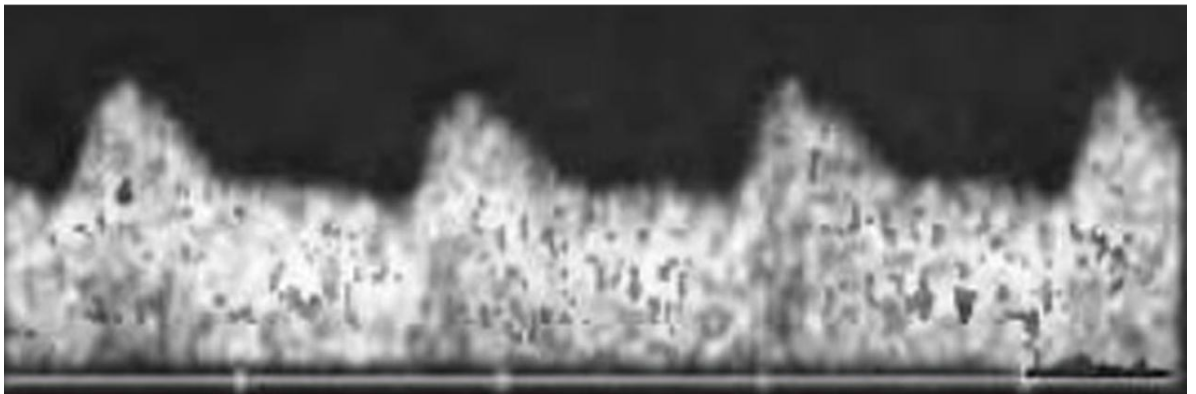

15 weeks

Image (2): 15 week with no blood flow

Image (3): 20 week with diastolic notch
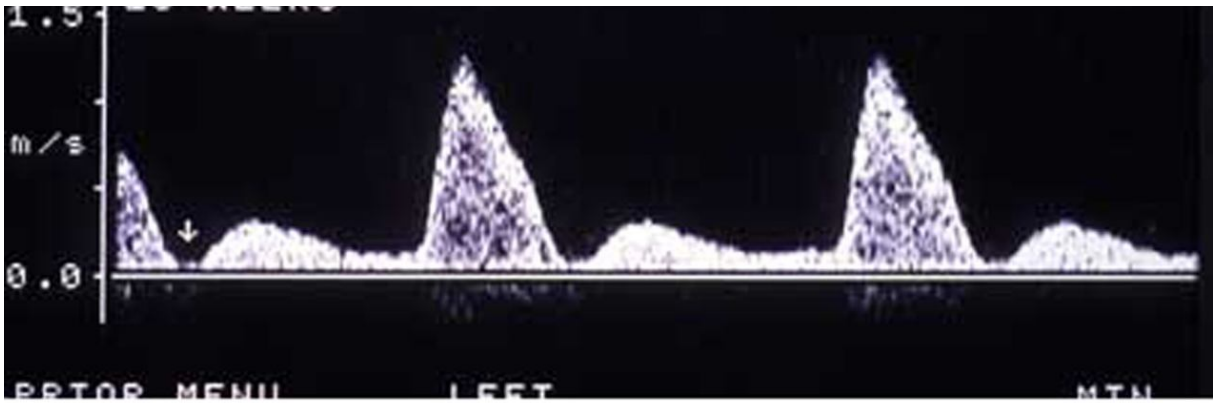

Image (4): 22 week with diastolic notch
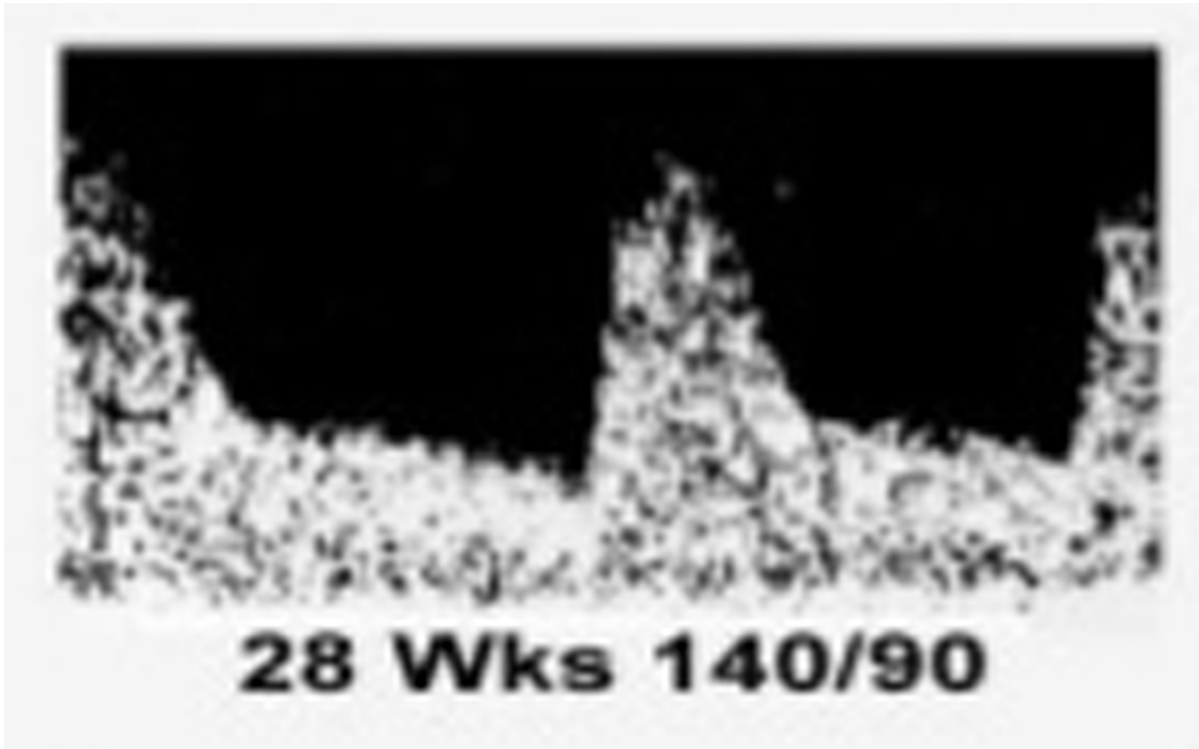
Image (5): 24 week with diastolic flow

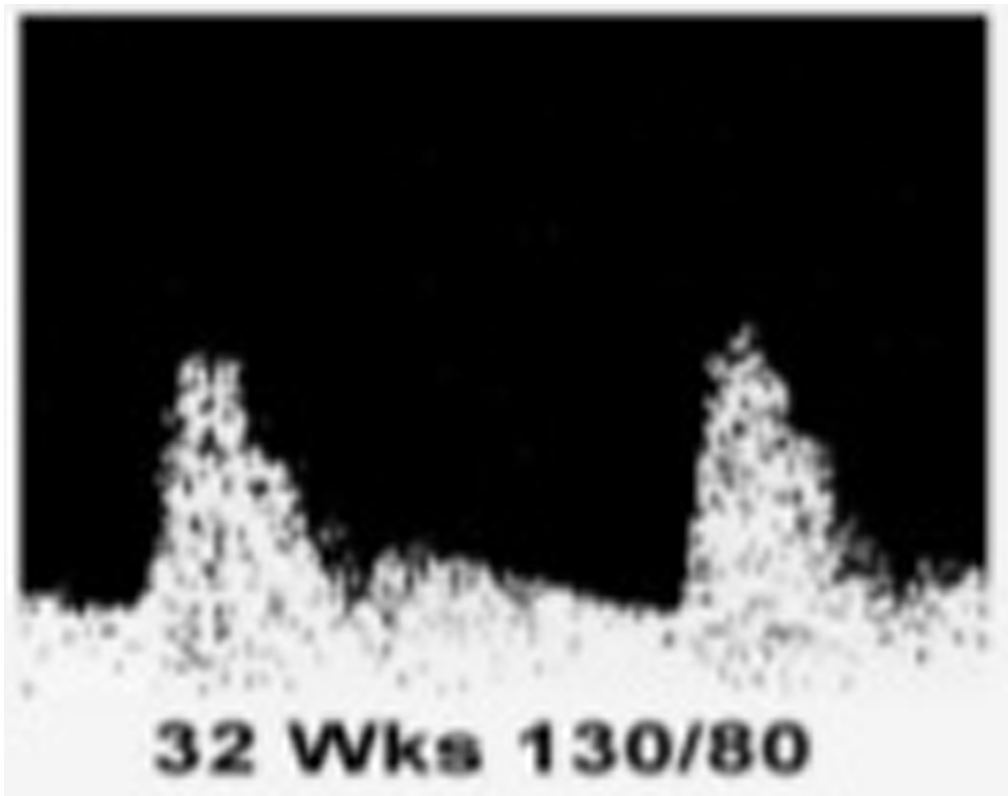Image (6): 28 week with diastolic flow

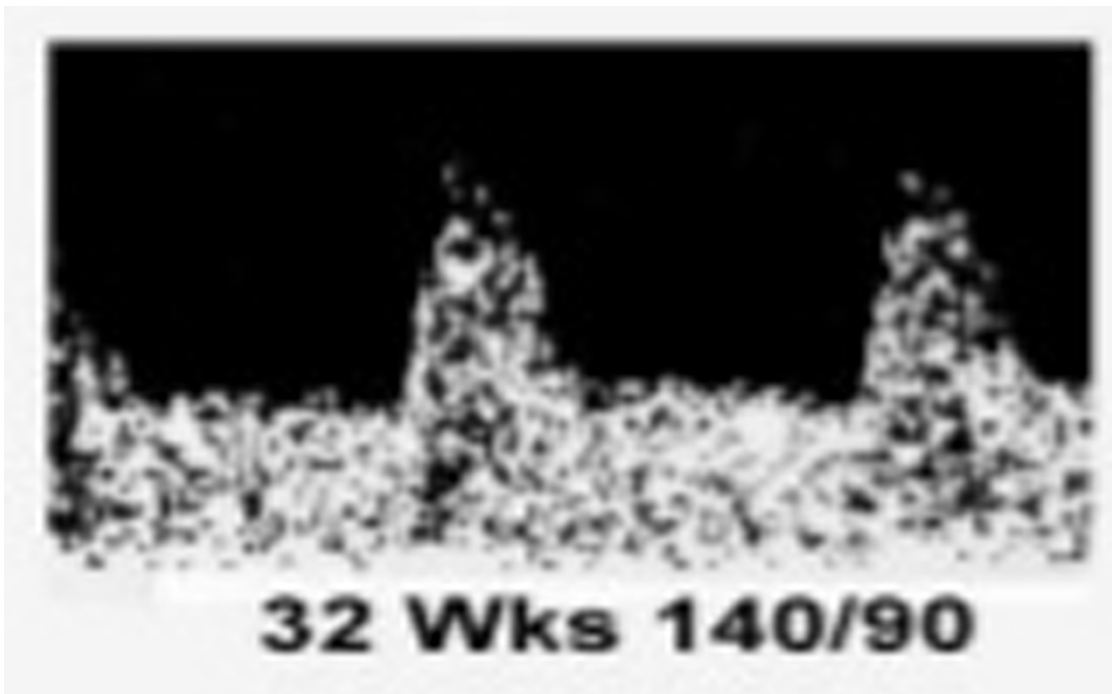Image (7): 32 week with moderate pre-eclampsia

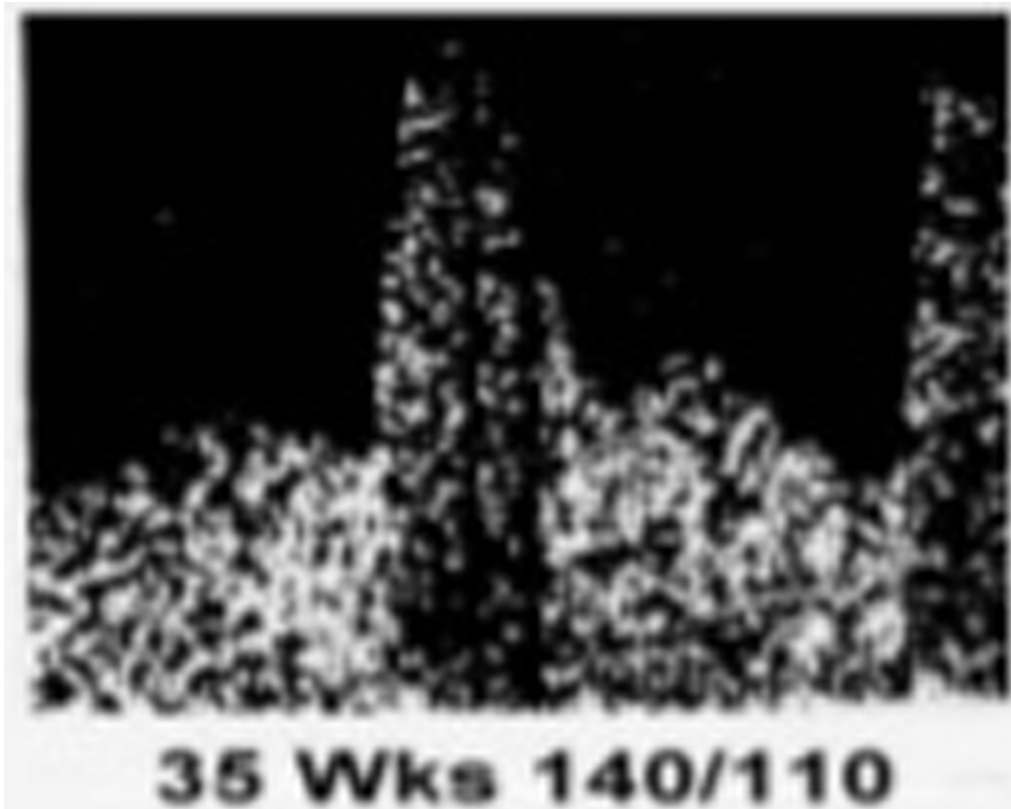Image (8): 32 week with moderate pre-eclampsia

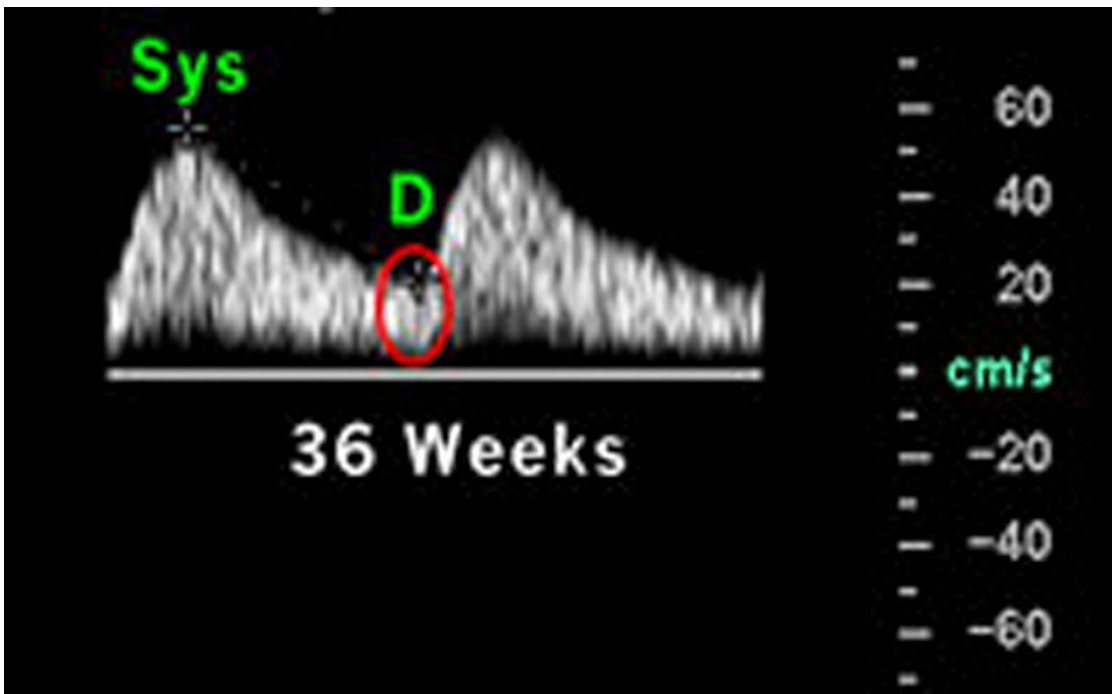Image (9): 35 week with moderate pre-eclampsia

Image (10): 36 week with moderate pre-eclampsia

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