"A STUDY OF PLACENTAL HISTOPATHOLOGICAL CHANGES IN IDIOPATHIC TERM IUGR PREGNANCIES"

By

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In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY

IN

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"**A STUDY OF PLACENTAL HISTOPATHOLOGICAL CHANGES IN IDIOPATHIC TERM IUGR PREGNANCIES**"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. MUNIKRISHNA. M**, Professor & Head, Department of Obstetrics and Gynaecology, Sri Devaraj Urs Medical College, Kolar, in partial fulfilment of University regulation for the award "**M.S. DEGREE IN OBSTETRICS AND GYNAECOLOGY**", the examination to be held in April, 2017 by SDUAHER. This has not been submitted by me previously for the award of any degree or diploma from the university or any other university.

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Last but not least I would like to express my gratefulness to the almighty who has helped me to successfully complete this study.

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LIST OF ABBREVIATIONS

IUGR – Intra Uterine Growth Restriction

FGR – Fetal Growth Restriction

PAI – Plasminogen Activator Inhibitors

TSH – Thyroid Stimulating Hormone

FSH – Follicle Stimulating Hormone

LH – Leutinising Hormone

PI – Pulsatility Index

RI – Resistance Index

SD – Systolic Diastolic

CPR – Cerebro Placental Ratio

SGA – Small for Gestational Age

LBW – Low Birth Weight

BPD – Bi-Parietal Diameter

HC – Head Circumference

AC – Abdominal Circumference

FL – Femur Length

USG – Ultrasonography

POG – Period Of Gestation

EFW – Estimated Fetal Weight

AFI – Amniotic Fluid Index

RCOG – Royal College of Obstetrics and Gynaecology

ACOG – American College of Obstetrics and Gynaecology

ABSTRACT

Introduction: Intrauterine growth restriction (IUGR) is the inability of a fetus to maintain expected growth leading to fetal weight <10th percentile for gestational age. Fetal growth retardation is the second leading cause of perinatal morbidity and mortality.

Aims and objectives:

To study the placental histopathological changes and Doppler findings in idiopathic term IUGR pregnancies.

To compare the placental histopathological changes in IUGR pregnancy with that of normal pregnancy.

Methodology: The prospective case-control study included 40 cases with idiopathic term IUGR pregnancies and 40 controls with normal term pregnancies from December 2014 to August 2016. All routine investigations along with USG, umbilical and middle cerebral arteries Doppler were done. Placenta was weighed and examined for gross changes and histopathological features.

Results: The baseline demographic data was similar in both the groups. Fundal height, mean period of gestation, estimated fetal weight and amniotic fluid index by USG were less when compared to controls. Umbilical artery PI was increased in 9 cases (22.5%) and SD ratio was increased in 2 cases (5%). Middle cerebral artery PI

was decreased in 5 cases (12.5%) and RI was decreased in 1case (2.5%). Cerebroplacental ratio was <1 in 7 cases (17.5%). Mean birth weight of cases (2 ± 0.3 Kgs), was reduced as compared to controls (2.8 ± 0.3 Kgs) and placental weight in cases (316.3 ± 62.5 gms) was lesser than in controls (470 ± 79.7 gms). There was significant difference between cases and controls in terms of placental histopathological changes like Intervillous fibrin deposits (10% vs 0%), Perivillous fibrin deposits (37.5% vs 2.5%), Syncytial knots (35% vs 15%) and infarction (10% vs 0%) respectively.

Conclusion: There was significant placental histopathological changes in cases (idiopathic term IUGR pregnancies) as compared to that of controls (normal term pregnancies).

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INTRODUCTION

Intrauterine growth restriction (IUGR) or fetal growth restriction (FGR) is defined as the inability of a fetus to maintain expected growth leading to sonographic estimated fetal weight $<10^{th}$ percentile for gestational age or actual birth weight $<10^{th}$ percentile for gestational age.[1]

Intra-uterine growth retardation contributes to almost two-thirds of low birth weight infants born in India (UNICEF, 2004). IUGR occurs in 5-10% of all pregnancies and is associated with significant perinatal and infant morbidity and mortality.

Fetal growth retardation is the second leading cause of perinatal morbidity and mortality.[2]

Suboptimal growth at birth is associated with impaired intellectual performance, cardiovascular and metabolic diseases in adulthood.[3]

At term, the neonatal mortality rate of IUGR infants is 1% compared to 0.2% in those infants with appropriate birth weights.[2,3]

Causes for IUGR are diverse and in nearly 30% of cases the cause is idiopathic.

In recent years, it is firmly believed that research on the placenta holds the key to better understanding of IUGR etiology.

In cases of Idiopathic IUGR pregnancies primary placental involvement is seen.[4]

The low birth weight may be explained by an altered distribution of fetal blood in the placenta as a result of different modes of arrangement of intracotyledonary vessels of placenta in complicated pregnancy.

This vascular arrangement may be hampering equal distribution of blood flow in the placenta, increasing the risk to the mother and fetus.[5]

It is also suggested that antenatal detection of IUGR by use of Colour Doppler and its antepartum surveillance can improve outcomes and also placental histopathology study will help to establish a cause.[6]

The histopathological findings of placenta in IUGR signifies restriction of maternal utero-placental blood flow leading to impairment of fetal growth.[5,6]

Hence it is important to detect the histopathological changes in placenta of IUGR pregnancies. If the study shows significant histopathological changes, further research studies can be planned to find out the cause/causes which may provide a lead to prevention of this condition.

AIMS AND OBJECTIVES

1. To study the placental histopathological changes and Doppler findings in idiopathic term IUGR pregnancies.

2. To compare the placental histopathological changes in IUGR pregnancy with that of normal pregnancy.

REVIEW OF LITERATURE

HISTORICAL REVIEW

In 1959, Realdus Columbus coined the term "Placenta" which in Latin means "Plakons" meaning a flat cake on a plate.

William Harvey (1651), described that the circulation of mother and fetus must be separate, flowing in opposite direction.[7]

Van Haller described circulation of arterial blood of mother into veins of fetus and vice versa.[7]

William Hunter first described the anatomy of placenta and Weber described about intervillous space.

Hubercht introduced the word "Trophoblast" that serves to nourish the embryo.[7]

Wislocki and Dempreyin published the electron microscopic appearance of placenta.[7,8]

Shanklin and Little published on morphological and histopathological features of placenta in relation to abnormalities of pregnancy, labour and fetal weight.[8]

Joseph Hyrtl (1810-1894) gave a decisive summary of placental anatomy.[9]

The healthy outcome of a pregnancy relies mainly on the placental function. The placenta is the only organ which is shared by two individuals and has its unique characteristics. The placenta provides a dual circulation where both blood of mother and fetus flows through it. The placenta enables the nutrient and oxygen exchange from mother to the fetus.[10] A malfunctioning placenta can therefore affect the fetal well being and adds to the morbidity and mortality of the fetus.

DEVELOPMENT OF PLACENTA

The fertilization of the ovum takes place in the fallopian tube and reaches the uterine cavity as a morula, which is rapidly converted into a blastocyst and looses its surrounding zona pellucida. The outer layer of blastocyst proliferates to form trophoblastic mass. The trophoblast attaches itself to and invades a tissue it comes in contact with. Once the zona pellucida disappears, the cells of trophoblast sticks to uterine endometrium. This is called "Implantation".

This process of implantation is completed by 10^{th} – 11^{th} postovulatory day. After implantation of the embryo, the uterine endometrium is called decidua. The portion of the decidua that separates the embryo from the uterine lumen is called decidua capsularis and the part lining the rest of uterine cavity is called decidua parietalis.

At 10^{th} – 13^{th} postovulatory day, a series of intercommunicating clefts or lacunae appear in the rapidly enlarging trophoblastic cell mass. The functional elements of placenta are very small finger like process called villi. The villi are formed as off shoots from the surface of trophoblast. Trophoblast along with underlying extra embryonic mesoderm constitutes the chorion, the villi arising from it are called chorionic villi.

Hamilton et al[11] and Boyd et al[12] described the inter-relationship of normal fetuses and their placentas through various stages of intra-uterine life.

ANATOMY OF TERM PLACENTA

The human placenta is called as "HAEMO CHOREAL". It is a discoid organ measuring 15-20cm in diameter, 1.5cm in thickness and weighing 450-500 grams. The term placenta can show many gross and microscopic degeneration which is a part of physiological sequence of evolution. The placenta has 2 surfaces, fetal surface called placental roof/ shiny Schultz and maternal surface called dirty Duncan/ placental floor.

The placenta proper comprises of the chorionic villi with a thin decidual plate on maternal surface and chorionic plate on fetal surface. The maternal surface is divided by depressions of varying depth into a number of irregularly shaped areas called cotyledons.

Section through the placenta from fetal to maternal surface shows following layers:

1. Amnion
2. Chorionic plate
3. Villi
4. Decidual septa
5. Decidua basalis made up of compact and spongy layer.

Sinclair[13] observed that placental weight increased linearly as gestation progressed. According to Little[14], normal placental co-efficients defined by the ratio of weight of placenta to the weight of the fetus was between 0.10 and 0.18. Values less than 0.08 and more than 0.2 were considered abnormally small and abnormally large respectively.

Gruenwald et al[15] studied 1232 normal deliveries and concluded that size of the baby did not depend on placental weight though the placental weight determines its function alone.

Aherne and Dunnill,[16] studied the quantitative aspects of placental structure. They observed the volume proportions of villi and total surface areas by counting points and used linear intercept methods. They observed that at term, placentas of IUGR pregnancies had reduced mean volumes compared to that of normal pregnancies. Significant deficit of parenchyma was studied: the villous surface area and fetal capillary surface area in the placentas of IUGR pregnancies were evidently lower than normal pregnancies. They suggested that primary placental hypoplasia may lead to stunting.

Placental membrane :

The mixing up of maternal and fetal blood is separated by placental membrane made up of the layers of the wall of the villi. These are (from fetal side) :-

1. The endothelium of blood vessel and its basement membrane
2. Surrounding mesoderm (connective tissue)
3. Cytotrophoblast and its basement membrane
4. Syncytiotrophoblast.

These structures constitute the placental barrier. Exchange of oxygen, nutrition and waste products takes place through this membrane.

The villus of the placenta were classified based on its size, stromal characteristics and vessel structure into stem villi, mature intermediate villi, terminal villi, immature intermediate villi and mesenchymal villi.[17] The extremely attenuated syncytiotrophoblast covers the terminal villi forming the maternal- fetal exchange surface.[18]

Biswas et al[18] had similar observations and commented that idiopathic IUGR might be due to the reduction in the villous surface area.

Placental weight is the most common way to characterize placental growth, but it is a summary of many dimensions of growth, including laterally expanding growth of the chorionic disc and chorionic disc thickness.

Benirschke and Kaufmann[19] suggested that early infarct may also contribute to an irregular placental shape. Determination of placental shape is a relatively early gestational event.

The lateral expansion of the chorionic plate marks the area of the uterine lining overlaid by the placenta; as such, it determines the maximum number of uterine spiral arteries that can be converted to supply the placenta.[20] The chorionic plate also contains the high capacitance/low resistance vessels and thus marks aspects of the hemodynamic resistance presented to the fetal heart. If the chorionic plate is very small, there will be a reduced

chorionic vessel length compared with a larger chorionic plate, and thus there will be a net decrease in capacitance, and potentially an effect on resistance. The spiral arteries that could be tapped by trophoblast to supply the placenta may be limited.

Placental disk thickness is an indirect measure of the extent of nutrient exchange surface of the placenta, essential to its successful support of fetal growth. Progressive branching or arborization of the villous tree increases the thickness of the placental disk. However, there may reasonably be an optimal placental thickness that balances a healthy nutrient exchange surface with optimal intervillous perfusion. In normal placentas of normal thickness, subchorionic villi are already showing changes related to poor perfusion. In thicker placentas, the increased depth of villous arborization might therefore be less efficient. Abnormally thick placentas have been correlated with adverse pregnancy outcome.[21] This association may be due to abnormally large placental oxygen demands limiting the oxygen available to the fetus and abnormal intervillous stasis through an abnormally complex intervillous space. If the villous tree is too complex or too dense, intervillous perfusion may be more sluggish.

According to Thompson et al,[22] thicker placentas were more common in cases with absent end-diastolic umbilical arterial flow, a condition in which forward flow of blood in the umbilical cord to the placenta ceases during fetal cardiac diastole.[19]

Salafia et al,[23] have studied that increased disk thickness reduces placental efficiency by several processes:-

1. By reducing efficiency of maternal intervillous perfusion through an abnormally complex intervillous space.
2. By increasing placental metabolic maintenance requirements.
3. By increasing placental resistance resulting in increased fetal heart work.

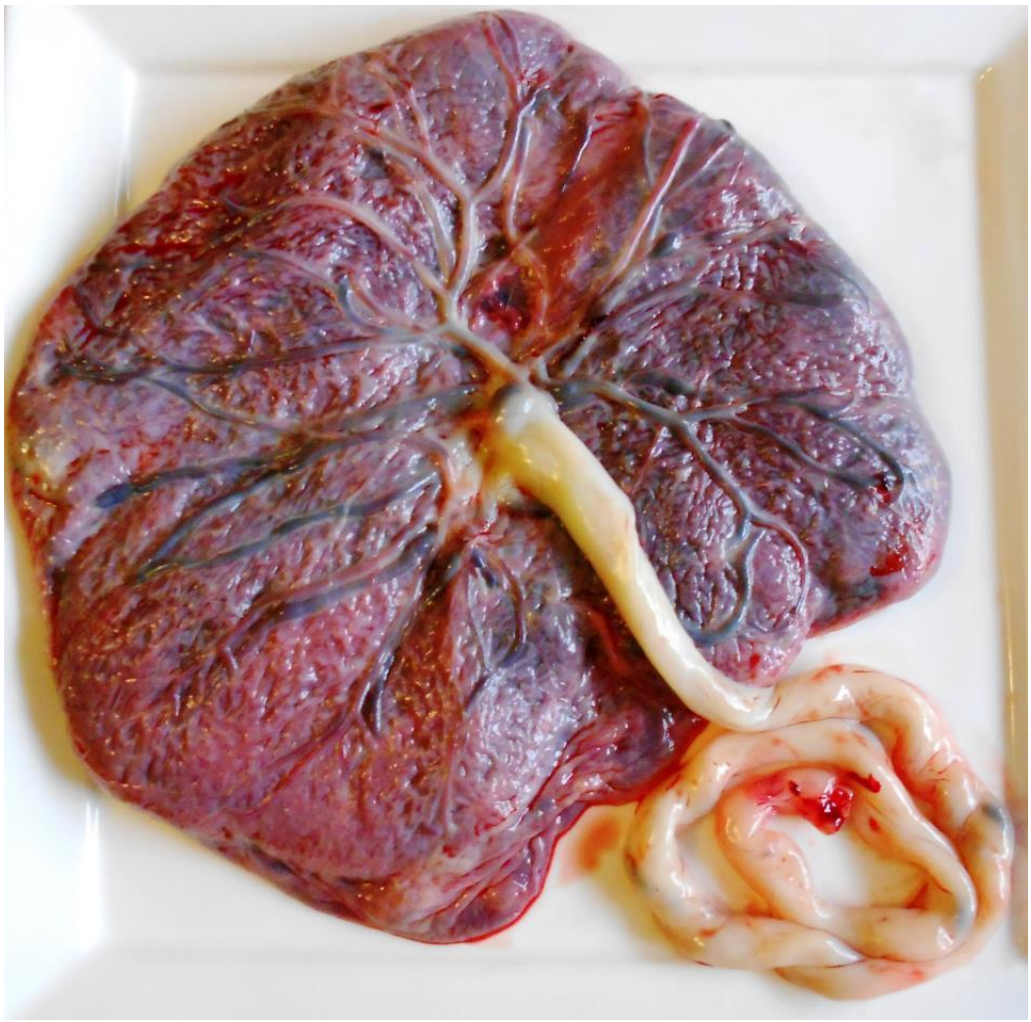


Figure 1 : Gross picture of normal placenta

UTERINE VASCULAR ADAPTATION OF PREGNANCY:

The anastomosing uterine and ovarian arteries give rise to a series of arcuate vessel, which penetrate the myometrium and form a complex anastamosing network. These inturn give rise to radial arteries, which extend immediately beneath the basal endometrium where they divide into smaller basal arteries, which supply the adjacent myometrium and basal endometrium and then further divide into large spiral arteries, which supply the remaining endometrium. The spiral arteries are hormone responsive vessel, which undergo cyclical changes throughout the menstrual life.

The spiral arteries undergo profound physiological modification following implantation and during placentation. Modification to the spiral arteries affects the segment of vessels in decidua basalis, which lies beneath chorion frondosum.

The cytotrophoblast invade the decidua occurring in singles or in groups.

During the middle of 2nd trimester, second wave of endovascular trophoblastic invasion occurs and the remaining portion of spiral artery and terminal segment of radial artery within the myometrium undergo similar adaptive modification, these changes extending proximal to the origin of the basal arteries. The end result is progressive distension of spiral arteries to form the uteroplacental arteries, a reduction in vascular resistance and profound increase in the blood flow.

According to Sheppard BL and Bonnar J,[24] the uteroplacental circulation comprises of various hemostatic changes during pregnancy. Uterine spiral arteries undergo physiological adaptations in order to accommodate the increased maternal blood flow to the intervillous space of the placenta and this adaptation is induced by the invading endovascular trophoblast cells. The arterial walls in the uteroplacental circulation are made of trophoblasts, fibrin or fibrinoid which replaces most of the vascular endothelium and the underlying medial smooth

muscle. Plasminogen activator inhibitors (PAI-1 and PAI-2) present in high levels in the decidual spiral arteries have reduced capacity to lyse fibrin. This leads to increased fibrin deposition and reduced uteroplacental circulation in pregnancy. In pregnancies complicated by IUGR the fibrin deposition is accentuated as a result of increased production of PAI-1 and this coupled with physiologically maladapted spiral arteries results in reduced uteroplacental blood flow. Recent studies have shown PAI-1 levels were higher in the placenta and uterine vein in IUGR complicated pregnancies. The cytotrophoblast cells in IUGR placenta express high levels of PAI-1 which restricts the trophoblast invasion in early pregnancy.

Thompson et al[25] and Baschat et al,[26] studied that Uteroplacental function is governed by 3 primary components: (1) the intervillous spaces perfused by the maternal uteroplacental circulation (2) the trophoblast of placenta (3) the fetoplacental circulation that includes placental vessels in close relation with the fetal vasculature. The fetoplacental circulation has been demonstrated to be most highly related to adverse outcomes.

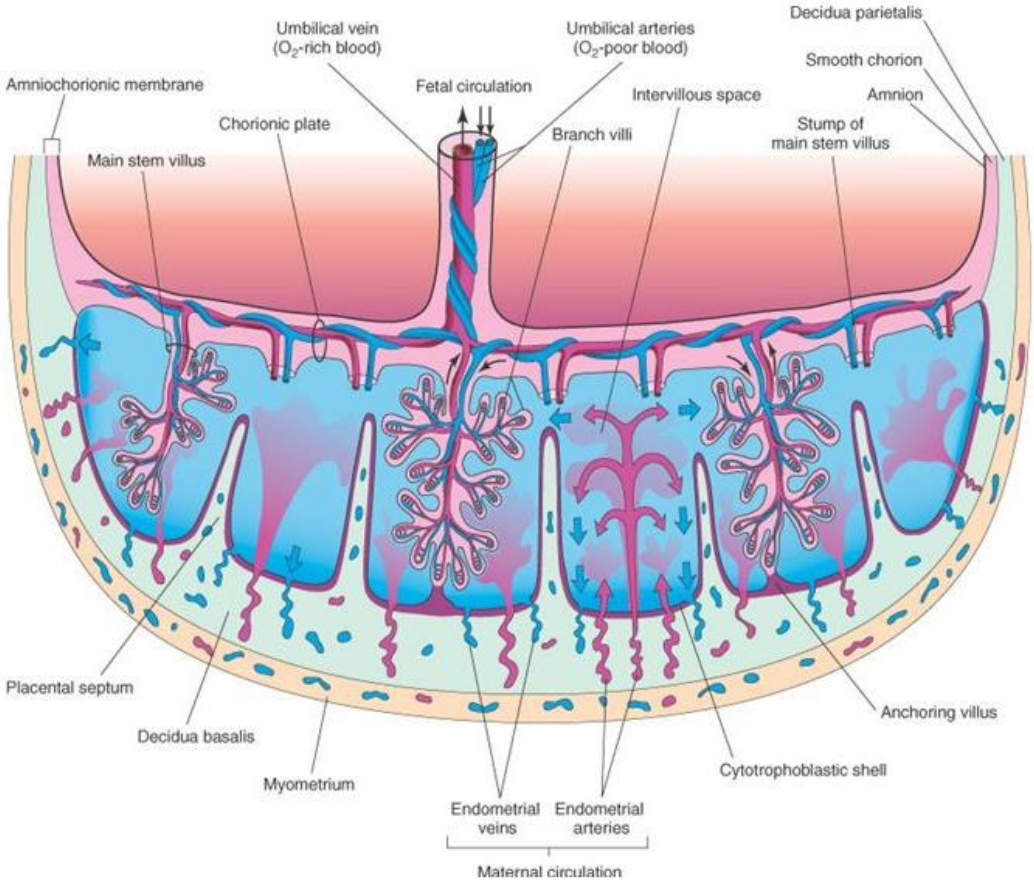


Figure 2 : Schematic diagram showing Uteroplacental circulation

THE FETAL CIRCULATION THROUGH THE PLACENTA:

The basic anatomical unit of mature placenta is a fetal cotyledon or lobule, which consists of a group of stem, terminal and anchoring villi, which are supplied by the fetal circulation by branches of the umbilical arteries and drain into a branch of the umbilical vein. These branches arise and terminate in the chorionic plate.

Terminal branches of a single uteroplacental artery supply each fetal cotyledon and there are normally 100-150 such units in a term placenta. The fetal vessel in the villi plays only a minor role in trophoblastic survival, though the presence of circulation through them may be of critical importance. Uteroplacental arteries are considered as end arteries.

The maternal blood from these vessels enters the central region of fetal cotyledon where the villi are numerous and most densely packed. It flows to periphery completing the exchange of respiratory gases and metabolites and finally to maternal circulation via numerous decidual veins. By the end of pregnancy the intervillous space measures approximately 150ml, a volume of arterial blood which contains enough oxygen to supply the fetus for 60-90 seconds.

In normal pregnancies, fetoplacental vascular resistance decreases as gestation progresses.[27] This occurs due to the formation of new vascular conduits from 20 weeks through term gestation by both branching and nonbranching angiogenesis.[28] In FGR placentas the high fetoplacental resistance is mainly due to the formation of increased nonbranching angiogenesis. Therefore, the formation of abnormally thin, elongated villous vessels are the end result of improper balance in branching and nonbranching angiogenesis which further results in elevated fetoplacental vascular resistance in FGR.[29]

According to Alfirevic et al,[30] Baschat AA[31] and Unterscheider J et al[32] abnormally elevated fetoplacental vascular resistance in FGR pregnancies, as evident by abnormal umbilical artery

Doppler velocimetry, gradually increases the risk for adverse perinatal outcomes, neurodevelopmental consequences and long-term health problems.

FUNCTIONS OF PLACENTA:

1. Transfer of nutrients and waste products between mother and fetus.

Mechanism involoved in the transfer of substances across placenta is simple diffusion, facilitated diffusion, active transport, pinocytosis, leakage.

A] Respiratory function – intake of oxygen and output of carbon dioxide takes place by simple diffusion across the fetal membrane.

B] Excretory function – waste products from the fetus like urea, uric acid, creatinine are excreted to maternal blood by simple diffusion.

C] Nutritional function – Glucose is the principle source of energy and is transferred to the fetus by facilitated diffusion. Lipids, sodium, potassium, chloride traverse by simple diffusion. Amino acids, calcium, phosphates, iron and water soluble vitamins are transported by active transport. Fat soluble vitamins are transferred slowly.

2. Placenta produces or metabolises the hormones and enzymes necessary to maintain pregnancy. Hormones produced are:-

a] Human chorionic gonadotropin

b] Human placental lactogen

c] Human chorionic thyrotrophin

d] Human chorionic corticotrophin

e] Pregnancy specific beta 1 glycoprotein

f] Estrogen, estriol, estrone

g] Progesterone

h] TSH releasing hormone

i] LH/ FSH releasing hormone

3. Barrier function – placental membrane is considered as protective barrier to the fetus against the noxious agents circulating in the maternal blood.

4. Immunological function – the fetus and placenta contains parentally determined antigen, foreign to the mother's antigen. Inspite of this there is no evidence of graft rejection. Placenta probably offers immunological protection against rejection. The exact mechanism though not known, has been centered on the following:-

- Fibrinoid and sialomucin coating of trophoblast may suppress the trophoblastic antigen.
- Development of specific mucoprotein mucopolysaccharide complex by the decidual cells.
- Placental hormones like steroids and chorionic gonadotrophin although have got weak immunosuppressive effect, may be responsible for producing sialomucins.
- Nitabuchs layer which intervenes between the decidua basalis and the cytotrophoblast probably inactivates the antigenic property of the placenta.

According to a study conducted by İskender-Mazman D et al,[33] IUGR babies had increased placental infarcts, increased syncytial knots and histiocytic intervillositis. They further described that chronic patterns of injury were found to be more than acute patterns in IUGR pregnancies. If the injury in the placenta is acute or mild, fetal adaptation can compensate and prevent fetal growth restriction.

Wigglesworth[34] demonstrated that placental infarct of more than 5% area had been a key factor in causing low birth weight.

Burton and Jones[35] described that syncytial knots normally accumulate on the villous surface until term, without any correlation to apoptosis or trophoblast turnover.

Heazell and Moll[36] found an increase in the number of syncytial knots in placentas of IUGR pregnancies.

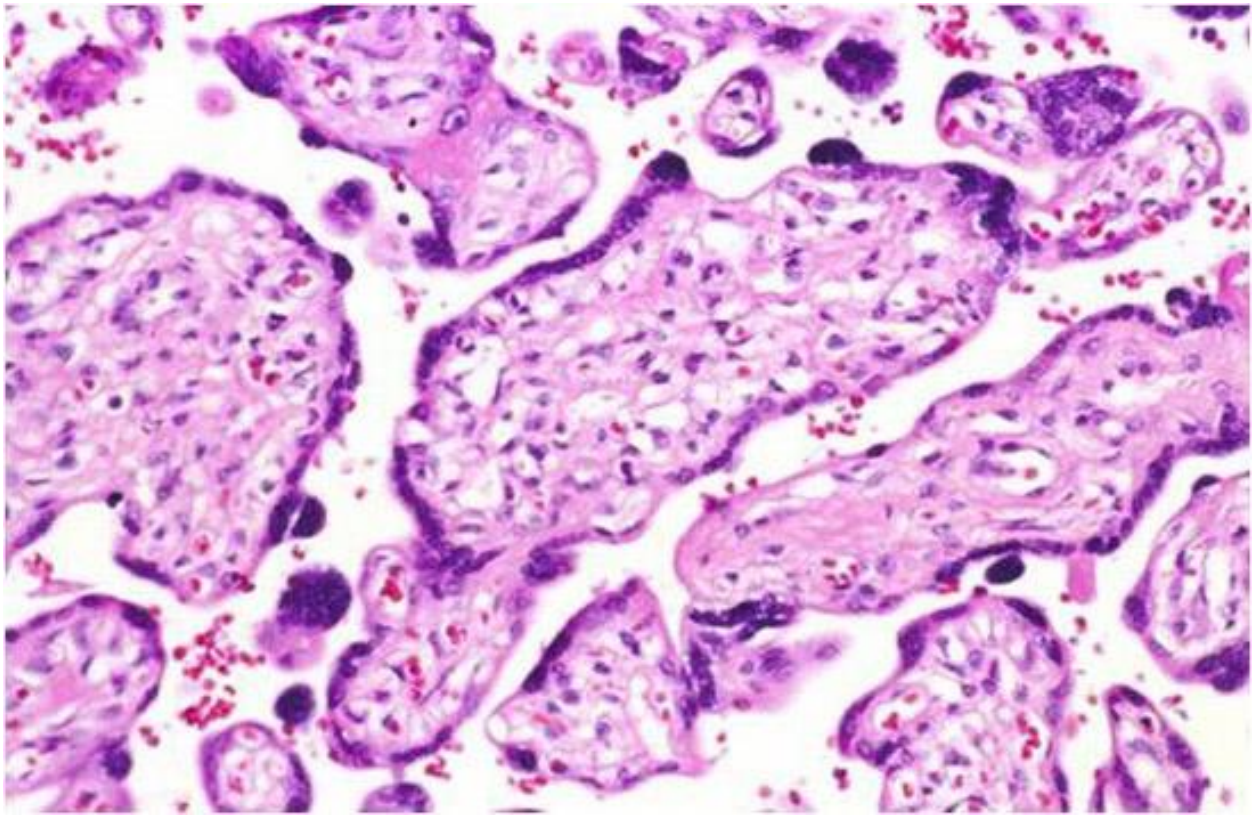


Figure 3 : Microscopic picture of normal placenta

COLOUR DOPPLER IN PREGNANCY

Doppler velocimetry of the uterine arteries reveals a progressive decrease in impedance with advancing gestational age.

According to Papageorghiou et al,[37] this decrease in impedance is thought to reflect a maternal adaptation to pregnancy resulting from trophoblastic invasion of the maternal spiral arterioles in the first half of gestation.

In early gestation, a notched uterine artery Doppler waveform and low diastolic flow is evident due to high vascular impedance.[38] With advancing gestation, decreasing vascular impedance is reflected by increased flow in diastole and disappearance of the notch. Persistence of notch in uterine artery Doppler in the late second and third trimesters has been used to identify abnormal uterine circulation in pregnancy.[39]

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

$$\text{Resistance Index (RI)} = \frac{\text{Peak systolic velocity} - \text{End diastolic velocity}}{\text{Peak systolic velocity}}$$

$$\text{Systolic/Diastolic(SD) ratio} = \frac{\text{Peak systolic velocity}}{\text{End diastolic velocity}}$$

Doppler velocimetry of the umbilical artery assesses the resistance to blood perfusion of the fetoplacental unit. As early as 14 weeks, low impedance in the umbilical artery allows continuous forward flow throughout the cardiac cycle. Maternal or placental conditions that

obliterate small muscular arteries in the placental tertiary stem villi result in a progressive decrease in end-diastolic flow in the umbilical artery Doppler waveform until absent and then reversed flow during diastole are evident.[40]

Absent or reversed end diastolic flow in the umbilical artery is usually associated with severe IUGR and oligohydramnios. Reversed end diastolic flow in umbilical artery circulation represents an advanced stage of placental compromise and has been associated with obliteration of >70% of arteries in placental tertiary villi.[41]

Normal range of Umbilical artery Doppler in term gestation :

- Pulsatility index : 0.8 – 0.9
- SD ratio : 2 – 3.5

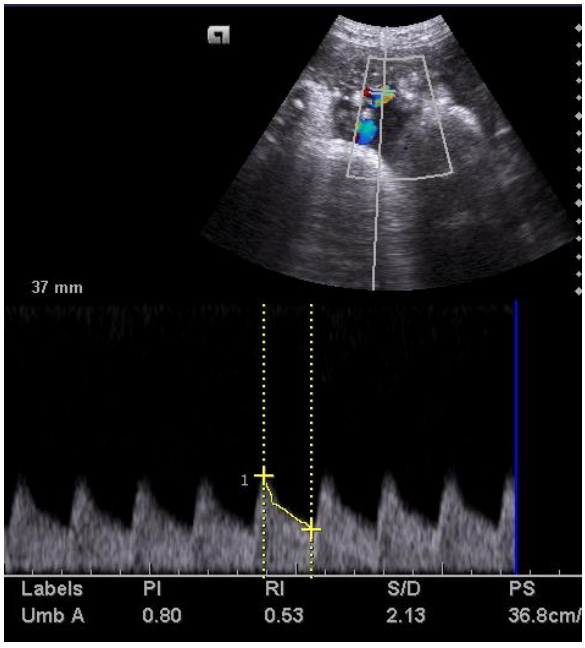


Figure 4 : Normal Umbilical Artery Doppler

Under normal conditions, the cerebral circulation is a high impedance circulation with continuous forward flow present throughout the cardiac cycle. The middle cerebral arteries, which carry >80% of the cerebral circulation, represent major branches of the circle of Willis and are the most accessible cerebral vessels for ultrasound imaging in the fetus.[42] In the presence of fetal hypoxemia, central redistribution of blood flow results in increased blood

flow to the brain, heart and adrenal glands and a reduction in flow to the peripheral circulations. This blood flow redistribution, known as the brain-sparing reflex, is characterized by increased end-diastolic flow velocity (reflected by a low PI and RI) in the middle cerebral artery.[4]

Normal range of Middle Cerebral artery Doppler in term gestation :

- Pulsatility index : 1.2 - 1.5
- Resistance index: 0.7 – 0.8

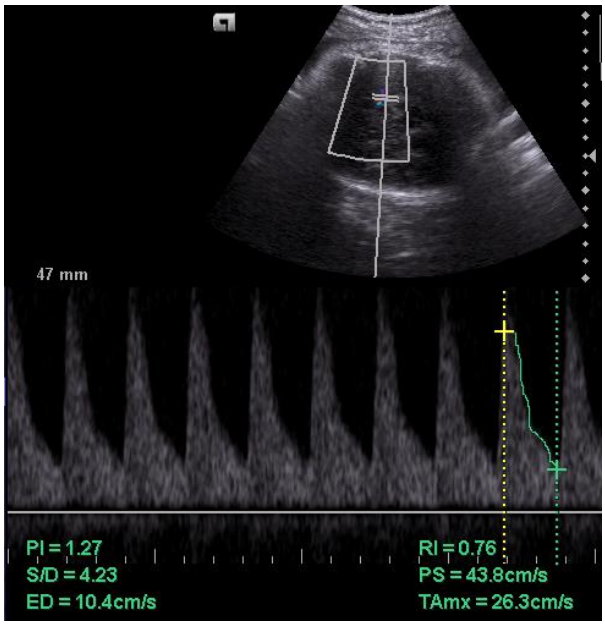


Figure 5 : Normal Middle Cerebral Artery Doppler

Doppler assessment of brain sparing can also be assessed with the cerebroplacental ratio, which is defined as middle cerebral artery PI/ umbilical artery PI. A fetus is considered to have brain sparing when this ratio is <5th percentile for gestational age.[42,43]

$$\text{Cerebro Placental Ratio (CPR)} = \frac{\text{Middle cerebral artery PI}}{\text{Umbilical artery PI}}$$

INTRAUTERINE GROWTH RESTRICTION

Intrauterine growth restriction (IUGR) is defined as fetal growth less than the normal growth potential of a specific infant because of genetic or environmental factors. IUGR is a clinical definition and applied to neonates with clinical evidences of malnutrition.

IUGR refers to weight below the 10^{th} percentile for gestational age, corrected for parity and gender, as per the population growth charts.

It can be further classified as:-[44]

• Moderate: Birth weight in the 3^{rd} to 10^{th} percentile

• Severe: Birth weight less than 3^{rd} percentile

Ponderal Index[45] is also used to determine the degree of fetal malnutrition.

It is defined as the ratio of body weight to length expressed as

(Ponderal Index = [weight (in g) x 100]÷[length (in cm)^3]).

Ponderal Index of less than 10^{th} percentile reflects fetal malnutrition and less than 3^{rd} percentile indicates severe fetal wasting. In term infants, Ponderal Index less than 2.2 and Mid Arm/ Head Circumference (MAC/HC) less than 0.27 are also considered as features of fetal malnutrition.

CLINICAL ASSESSMENT OF NUTRITION SCORE (CAN SCORE)

Metcoff J,[46] developed a scoring system, CAN score, for the assessment of nutritional status of the newborns at birth. Examination of hair, cheeks, chin, neck, chest, abdomen, back, arms, legs and buttocks is performed to assess the nutritional status of a newborn. CAN score of less than 25 implies malnourishment in a neonate.

CLASSIFICATION

There are 3 types of IUGR[47]

1. Symmetrical IUGR (Hypoplastic small for date)

Symmetric growth restriction begins early in gestation. Cell number is reduced. Caused by intrinsic factors such as congenital infections or chromosomal abnormalities. Infants with symmetric growth restriction have reductions in all parameters including weight, length and the head circumference. In such cases there will be less than 3 cm difference between the head and the chest circumference. Ponderal Index is more than 2.

2. Asymmetrical IUGR (Malnourished babies)

Asymmetric growth begins in the late second or third trimesters. The cell numbers are normal but cell size is reduced. Placental disorders cause metabolic derangements like reductions in fetal nutrients that limit glycogen and fat storage and also reduction in the weight and length. Babies will have loose skin fold, loss of buckle fat, featuring aged people

Ponderal Index is less than 2.

3. Mixed IUGR

Mixed IUGR describes the combined features of both symmetrical and asymmetrical IUGR. Here, along with the number of cells, the size of each cell will also be reduced. It occurs in late pregnancy when IUGR is affected by placental causes. The neonatal survival and neurodevelopmental growth is better in infants with normal cell numbers.

CEPHALIZATION INDEX:

Cephalization index was coined by Harel et al.[48] It is the ratio of head circumference to body weight. IUGR is severe when the head circumference: body weight ratio is high. Neurodevelopmental outcome like cerebral palsy and severe psychomotor retardation was increased with higher cephalization index. The cephalization index was a useful screening device for categorizing an IUGR infant based on severity.

CAUSES:

Several factors like maternal, fetal or placental may lead to Intrauterine growth restriction. Most of them are due to genetic causes or will be related to the fetal environment.

I] Maternal factors[49] :-

- Both extremes of age
- High altitude
- Lower socioeconomic status
- Maternal substance abuse - cigarette smoking, alcohol consumption, drug use.
- Exposure to drugs like warfarin, steroids, anticonvulsants, antineoplastic agents, anti-metabolite, folic acid antagonists.
- Nulliparity or grand multiparity
- Previous delivery of IUGR baby
- History of infertility treatment
- Poor antenatal care
- Poor maternal nutrition
- Inadequate maternal weight gain

Kharrazi et al,[50] evaluated the magnitude and shape of the relations between the environmental factors like exposure to tobacco and adverse pregnancy outcomes.

Goel et al,[51] performed a cross-sectional study to know the effects of passive smoking on outcome in pregnancy.

Yang Q et al,[52] in their case-control study examined the association of maternal alcohol consumption with the risk of IUGR.

II] <u>Placental Causes</u>[53]:-

- Hematologic and immunologic disorders like systemic lupus erythematosus, sickle cell disease, anti-phospholipid syndrome
- Maternal medical disorders (nephropathy, collagen vascular disease)
- Preeclampsia and diabetes associated with vasculopathy
- Infection and parasite infestations such as TORCH, malaria, tuberculosis, urinary tract infections and bacterial vaginosis

Any mismatch between fetal nutritional or respiratory demands and placental supply can result in impaired fetal growth. Various causes include –

- Abnormal uteroplacental vasculature
- Thrombophilia-related uteroplacental pathology
- Avascular villi
- Decidual or spiral artery arteritis
- Multiple infarctions
- Syncytial knots
- Chronic inflammatory lesions
- Abruptio placenta
- Velamentous umbilical cord insertion

- Placental hemangioma
- Placental infections
- Multiple gestation (limited endometrial surface area, vascular anastomoses)
- Genetic causes include increased expression of placental endoglin gene and vascular endothelial growth factor

Robinson et al,[54] conducted a study assessing the role of placental trisomy in preeclampsia and intrauterine growth restriction.

Szentpéteri I et al,[55] described placental gene expression patterns of endoglin in Intrauterine Growth Restriction (IUGR) pregnancies compared to normal pregnancies

III] <u>Neonatal factors</u>[56]:-

- Multifetal gestation
- Chromsomal abnormalities like trisomy 18 and 13.
- Major congenital anomalies
- Congenital infections (TORCH)
- Genetic syndromes like Russell-Silver syndrome
- Fetal phenylketonuria, transient neonatal diabetes mellitus
- Metabolic disorders including agenesis of pancreas, congenital absence of islets of langerhans, congenital lipodystrophy, galactosemia, generalized gangliosidosis type I, hypophosphatasia, I-cell disease

IV] <u>Genetic Causes</u>[57]:-

Polymorphisms in maternal, placental and fetal genes affect the fetal growth. These genes code for proteins and hormones.

A] Placental genes –

- Homeobox Genes
- SERPINA3 Genes
- NEAT1 (Nuclear Paraspeckle Assembly Transcript 1) gene
- Placental Growth Factor (PlGF)
- Trophoblastic miRNAs (micro RNA)
- Apoptosis Bcl-2 and Bax gene
- Placental Insulin-like growth factor (IGF1 & IGF2) and the insulin like growth factor binding protein (IGFBP)
- Placental Gene of Epidermal Growth Factor (EGF)

B] Maternal genes -

- Increased level of Endothelin-1 and Leptin
- Visfatin
- Thrombophilia genes and IUGR

C] Fetal genes -

- Increased level of Protein S100B
- Genetic deletion of Igf1 (Insulin Like growth factor 1) and SHOX gene
- Genetic mutation in Igf1r (Insulin-like growth factors 1 receptor)

CLINICAL FEATURES:

Clinical features of IUGR newborns are unique[47]. They are -

- Weight $<10^{th}$ percentile for the gestational age
- Large anterior fontanelle
- Increased head circumference:body ratio in asymmetrical IUGR

- Skin folds are loose in the nape of neck, inter-scapular area, axilla and groins
- Absent buccal fat, shrunken face
- Small abdomen, thin umbilical cord
- Decreased skeletal muscle mass and subcutaneous fat tissue with thin arms and legs
- Reduced breast bud formation and immature labia majora/minora due to loss of subcutaneous fat in female newborns
- Long finger nails
- Large hands and feet with increased skin creases

PHYSICAL EXAMINATION:

All infants with features of IUGR[47] must be examined closely to identify features of chromosomal anomalies, TORCH infections and major malformations. Polyhydraminos, absent stomach bubble on x-ray and IUGR were seen in tracheo-oesophageal fistula. IUGR caused by TORCH infections manifest with hepatosplenomegaly, skin rash including blue berry muffin lesions, cataract, cloudy cornea, chorioretinitis and thrombocytopenia. Chromosomal anomalies lead to IUGR with facial dysmorphism, cardiac defects and skin crease abnormalities.

OUTCOME:

A] Immediate Mortality and Morbidities[47]:

Severe IUGR infants will have increased prevalence of meconium aspiration, perinatal asphyxia and persistent pulmonary hypertension. Immediate neonatal complications include hypothermia, hypoglycemia, hyperglycaemia, hypocalcaemia, polycythaemia, jaundice,

feeding difficulties, feed intolerance, necrotizing enterocolitis, late onset sepsis, pulmonary haemorrhage.

Deorari et al,[58] in their study on 144 SGA babies proved that the most common morbidities was hypoglycemia (17%) and polycythaemia (10%).

B] Long term morbidities:

IUGR infants are at risk for impaired growth and neurodevelopment. Subsequent disorders in adults may also result from Fetal Growth Restriction (FGR).

Padidela et al,[59] evaluated the neuro-behaviour of the babies that were born Appropriate for gestational age and Small for gestational age.

C] Long term Physical Growth:

Long term growth of IUGR infants depends on the cause of the growth retardation, nutritional intake, socioeconomic status and the social environment.

Neonates who had symmetrical IUGR at birth remain constitutionally small throughout life.

Those infants with asymmetrical IUGR will acheive their inherited growth potential with an optimal environment and adequate nutrition.[60]

Chaudhari et al,[61] evaluated LBW infants till their age of 18 years. The cohort of LBW infants consisted of preterm SGA (n=61), full term SGA (n=30) and preterm AGA (n=70) infants. Seventy one full term AGA infants were the controls. Their study showed that SGA babies had reduced physical growth compared to AGA infants.

D] Long term Neurodevelopmental Outcome:

IUGR infants compared with infants born appropriate for gestational age will have delayed milestones and are more prone for mental retardation. Intellectual and neurologic functions of

the IUGR infants is decided by any adverse perinatal events or association of any specific cause of IUGR. Symmetrical IUGR has a greater impact on neurologic function than asymmetrical IUGR. Hypoxic ischemic encephalopathy and hypoglycaemia further worsens neurocognitive development in IUGR babies.[62]

The IUGR children are more likely to have[63] -

- Lower scores on cognitive testing
- School difficulties or require special education
- Gross motor and minor neurologic dysfunction
- Behavioral problems (attention deficit hyperactivity syndrome)
- Growth failure
- Reduced strength and work capacity

Leitner Y et al,[64] conducted a prospective study to examine children with IUGR for the neurodevelopmental and cognitive difficulties which may provide a lead to detect early clinical predictors of these difficulties.

PREVENTION OF IUGR:

Social factors play a major role in Intrauterine growth restriction in developing countries. Fetal growth and development are determined by adolescent nutrition, pre-pregnancy weights, poverty, inter-pregnancy interval in low and middle income countries.[65] The interventions to improve maternal nutrition include [66]-

a) Balanced energy protein

b) Calcium supplementation

c) Multiple micronutrient supplementations

d) Preventive strategies for malaria in pregnancy

MATERIAL AND METHODS

- Study design : Case - Control Study
- Study duration : December 2014 to August 2016
- Study area : R.L. Jalappa Hospital and Research Centre
- Sample size : 40 women were included in cases group and 40 women in control group

Sample size calculation:

- The sample size of 40 per group is calculated based on difference between two proportions of villous infarction[67] by using this formula :

$$\text{Sample size} = \frac{r+1}{r}\frac{(p^*)(1-p^*)(Z_\beta + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

P1 = 0.14 (controls)

P2 = 0.34 (cases)

95% confidence levels

80% power

5% level of significance

- p* - Average proportion exposed = proportion of exposed cases + proportion of control exposed/2
- Zb - Standard normal variate for power = for 80% power it is 0.84.
- Za/2 - Standard normal variate for level of significance as mentioned in previous section.
- p1 – p2 - Effect size or different in proportion expected based on previous studies.
- p1 is proportion in cases and p2 is proportion in control.

INCLUSION CRITERIA :

- Age > 18 yrs and < 35 yrs
- Women with completed 37 to 42 weeks of gestation
- Clinically/ Ultrasonographically diagnosed IUGR babies
- Single intrauterine pregnancy

EXCLUSION CRITERIA :

- Medical disorders of pregnancy (Anemia, chronic hypertension, Preeclampsia, Eclampsia, Diabetes mellitus, Heart diseases)
- Fetal congenital malformations (Prenatally diagnosed by USG)
- Maternal infections

METHODOLOGY

- All pregnant women with completed 37 to 42 weeks of gestation admitted in labour room, delivering at R.L. Jalappa Hospital and Research Centre were taken up for study from December 2014 to August 2016.
- 40 women were included in cases group and 40 women in control group.
- Written informed Consent were taken from all subjects who were involved in the study.
- The women with Idiopathic term IUGR pregnancies fulfilling the inclusion criteria were included in the study group and women with term normal pregnancies were included as controls after taking detailed history and examination.
- Institutional Ethical Committee Clearance was obtained

- IUGR was further classified as-[44]

  Moderate: Birth weight in the 3rd to 10th percentile

  Severe: Birth weight less than 3rd percentile

- Routine investigations were done in all the women:-

  - Complete blood count
  - Blood group and Rh typing
  - Urine analysis
  - Random blood sugar
  - HIV, HBsAg, VDRL

- Ultrasonography was done on Seimens[R] Acuson X300 premium machine. Fetal biometric measurements (BPD, HC, AC, FL) were taken. Estimated fetal weight and period of gestation were noted. Sum of 4 quadrants amniotic fluid was taken in centimeter.
- Colour Doppler study of umbilical artery was done for PI and SD ratio. Similarly it was done for middle cerebral artery for PI and RI and finally Cerebroplacental ratio was calculated.

Collection and examination of placenta

The placenta with attached membranes and umbilical cord were collected soon after delivery, washed in running tap water so as to clean all blood. The placenta was fixed in 10% formalin. Gross examination of placenta was done for the presence of retroplacental clot, hemorrhage, infarction, calcification and umbilical vessel anomalies. Weight of the placenta was recorded. Representative tissue bits were processed for microscopic examination. All the slides were stained with Haematoxylin and Eosin stain and screened for the following histopathological features.

1. Hyalinization
2. Intervillous fibrin deposits
3. Perivillous fibrin deposits
4. Syncytial knots
5. Basement membrane thickening
6. Villous degeneration
7. Fibrinoid necrosis
8. Calcification

STATISTICAL ANALYSIS:

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test of Fischer's exact test** (for 2x2 tables only) was used as test of significance for qualitative data.

Continuous data was represented as mean and standard deviation. **Independent t test or Mann Whitney U test** was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram, Pie diagram and Scatter plots.

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

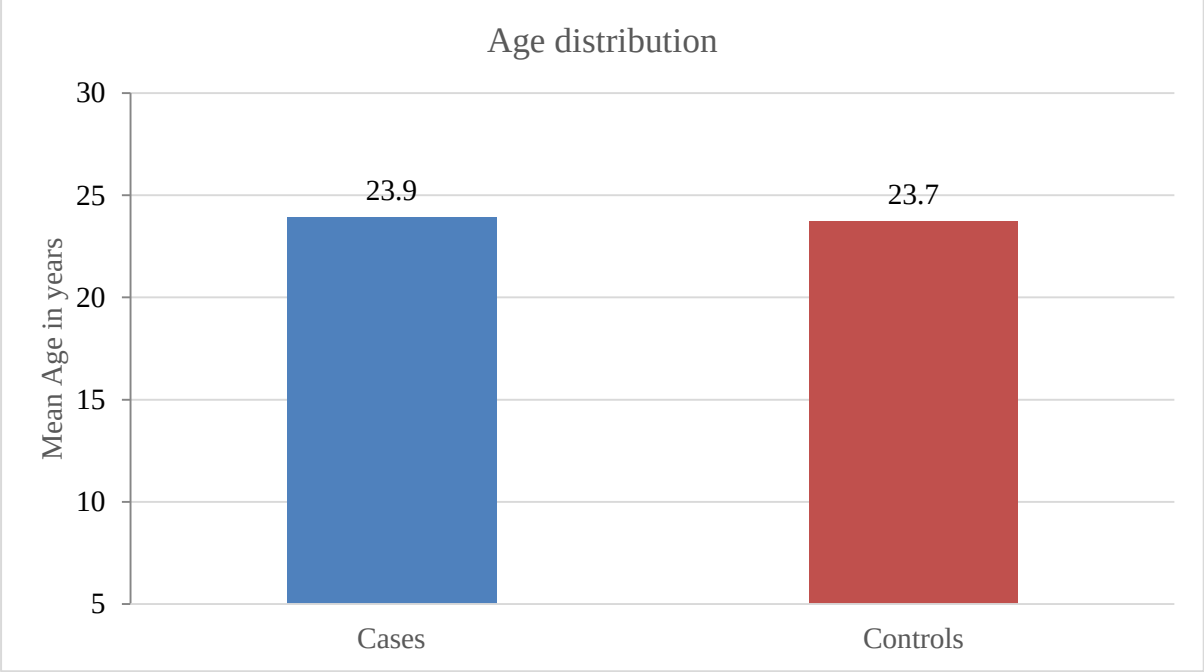
Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data. EPI Info (CDC Atlanta), Open Epi, Med calc and Medley's desktop were used to estimate sample size, odds ratio and reference management in the study.

RESULTS

Table 1: Age distribution

	Cases (n=40)		Controls (n=40)		p value
	Mean	SD	Mean	SD	
Age in years	23.9	4.2	23.7	3.8	0.781

Mean age of cases was 23.9 ± 4.2 years and controls was 23.7 ± 3.8 years. There was no significant difference in mean age between two groups.



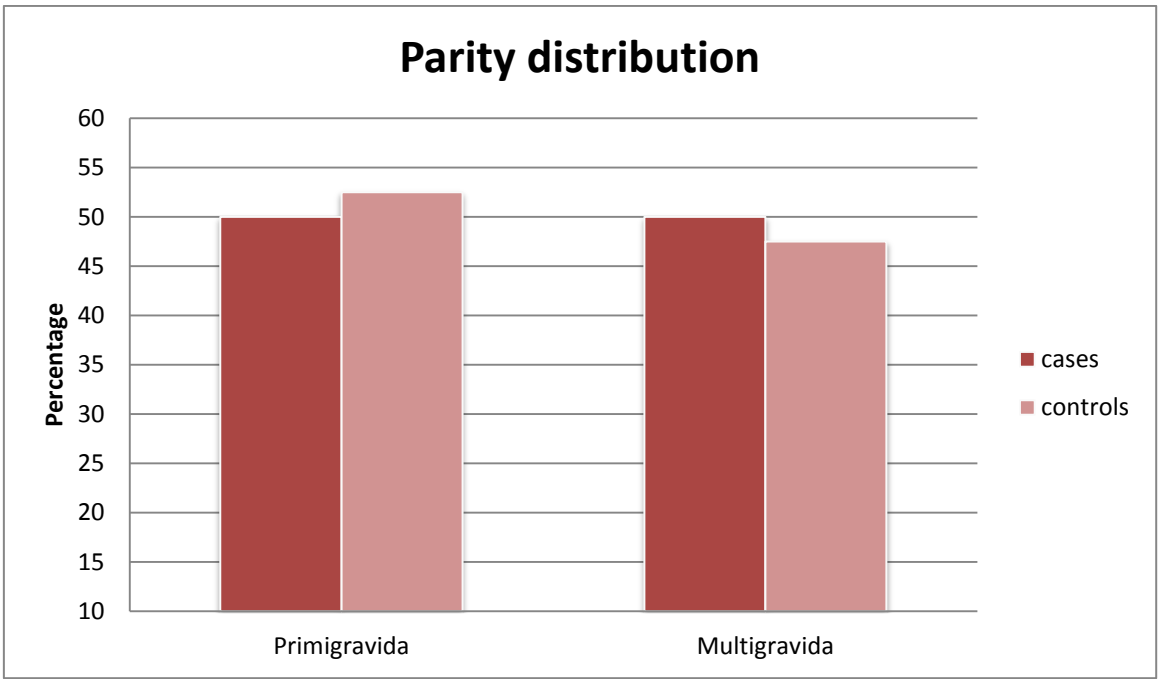
Graph 1: Bar diagram showing Age distribution

Table 2: Parity distribution

		Cases (n=40)		Controls (n=40)	
		Number	%	Number	%
Parity	Primigravida	20	50	21	52.5
	Multigravida	20	50	19	47.5
	Total	40	100	40	100

$\chi 2 = 0.05$, df = 1, p = 0.823

In cases 50% were Primigravida and 50% were Multigravida and in controls 52.5% were Primigravida and 47.5% were Multigravida. There was no significant difference in Parity between two groups. It means there is equal distribution or matching was achieved with respect to Parity.



Graph 2: Bar diagram showing Parity distribution between two groups

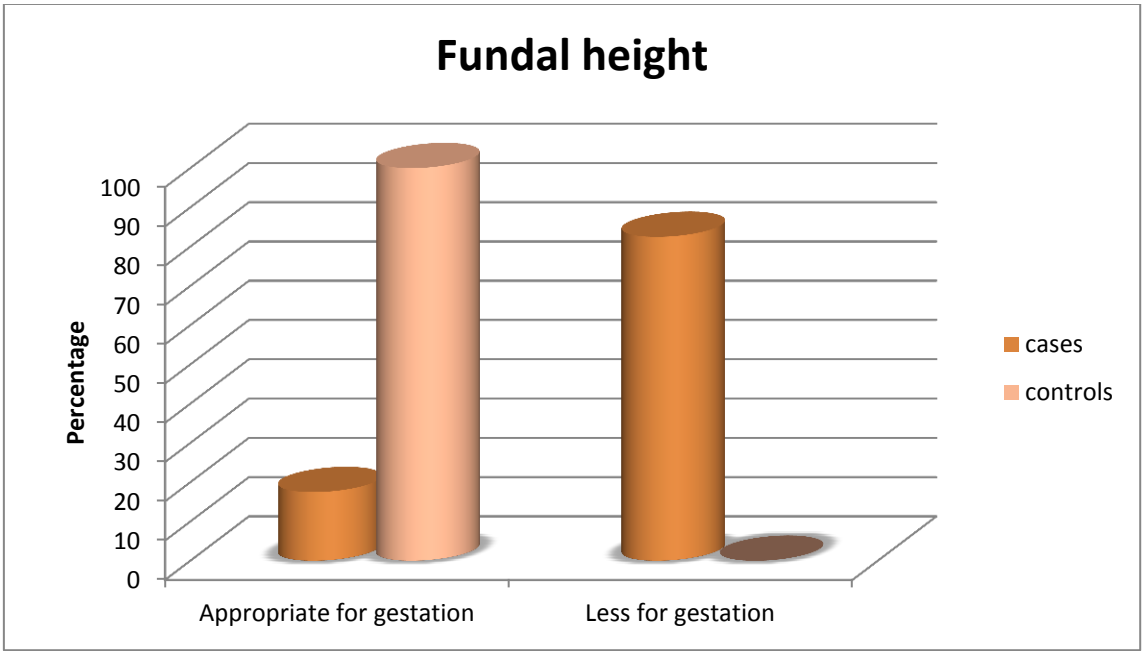
Table 3: Correlation of Fundal height between two study groups

		Cases (n=40)		Controls (n=40)	
		Number	%	Number	%
Fundal height	Appropriate for gestation	7	17.5	40	100
	Less for gestation	33	82.5	0	0

$\chi 2 = 56.17$, df = 1, p <0.001*

In cases 82.5% had clinically detectable growth lag on per abdomen examination and 17.5% had appropriate growth for gestational age. In controls none of them had growth lag.

*This observation was statistically significant.

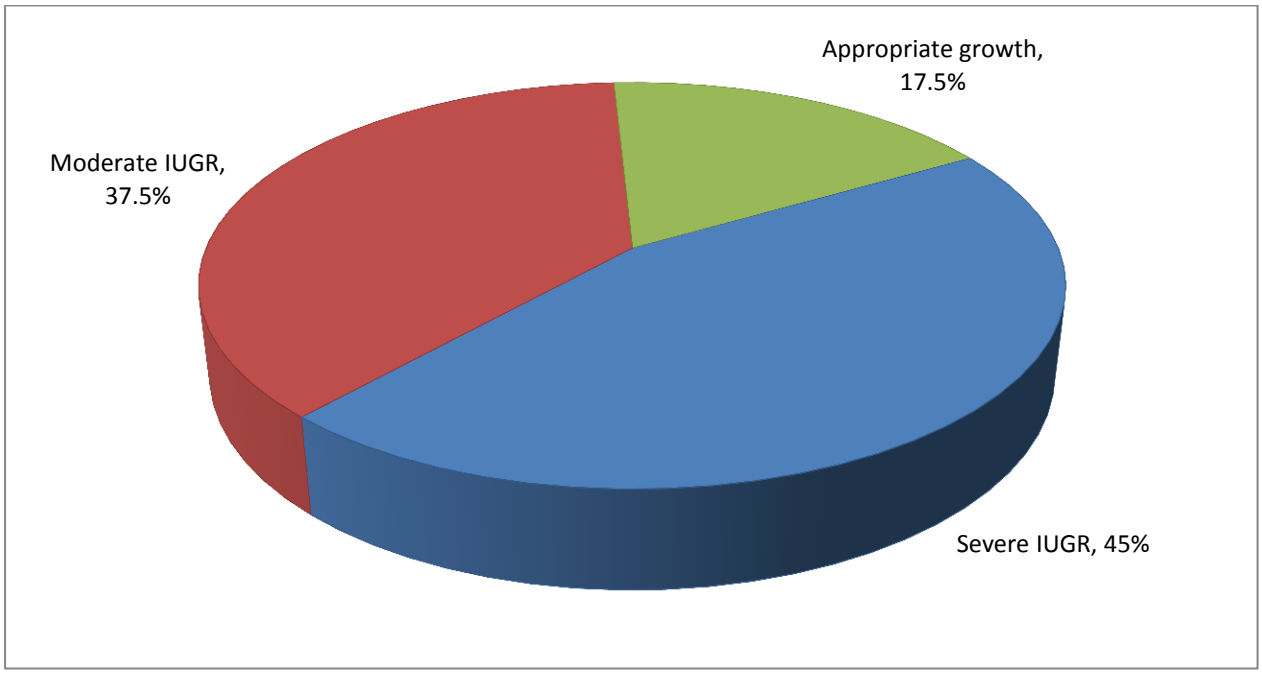


Graph 3: Bar diagram showing correlation of fundal height between two study groups

Table 4: Grading of IUGR based on Fundal height in cases

		Cases (n=40)	
		Number	%
Fundal height	Severe IUGR (6weeks lag)	18	45
	Moderate IUGR (4weeks lag)	15	37.5
	Appropriate for gestational age	7	17.5
Total		40	100

In Cases on per abdomen examination 45% had Severe IUGR with 6 weeks of growth lag, 37.5% had moderate IUGR with 4 weeks of growth lag and 17.5% had appropriate growth.

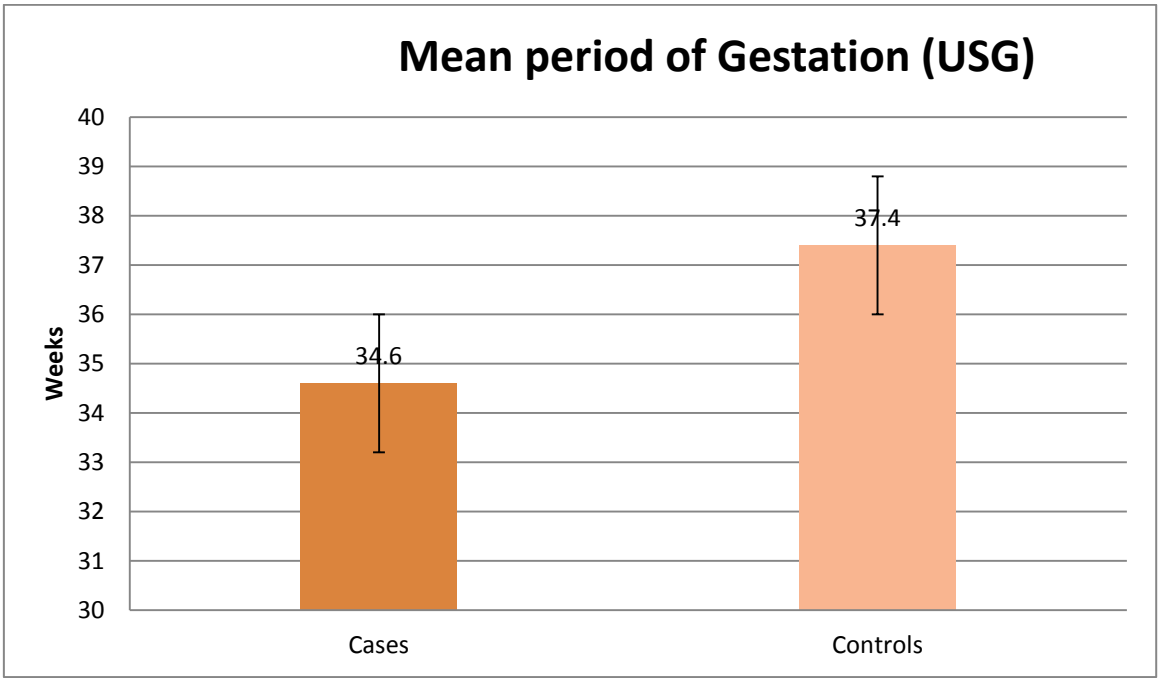


Graph 4: Pie diagram showing grading of IUGR based on fundal height in cases

Table 5: Mean Period of gestation between two study groups by USG at term

	Cases (n=40)		Controls (n=40)		p value
	Mean	SD	Mean	SD	
Period of Gestation by USG	34.6	1.9	37.4	1.5	<0.001*

Mean period of gestation by USG in cases was 34.6 ± 1.9 weeks and in controls it was 37.4 ± 1.5 weeks. *There was significant difference statistically in POG between two groups.

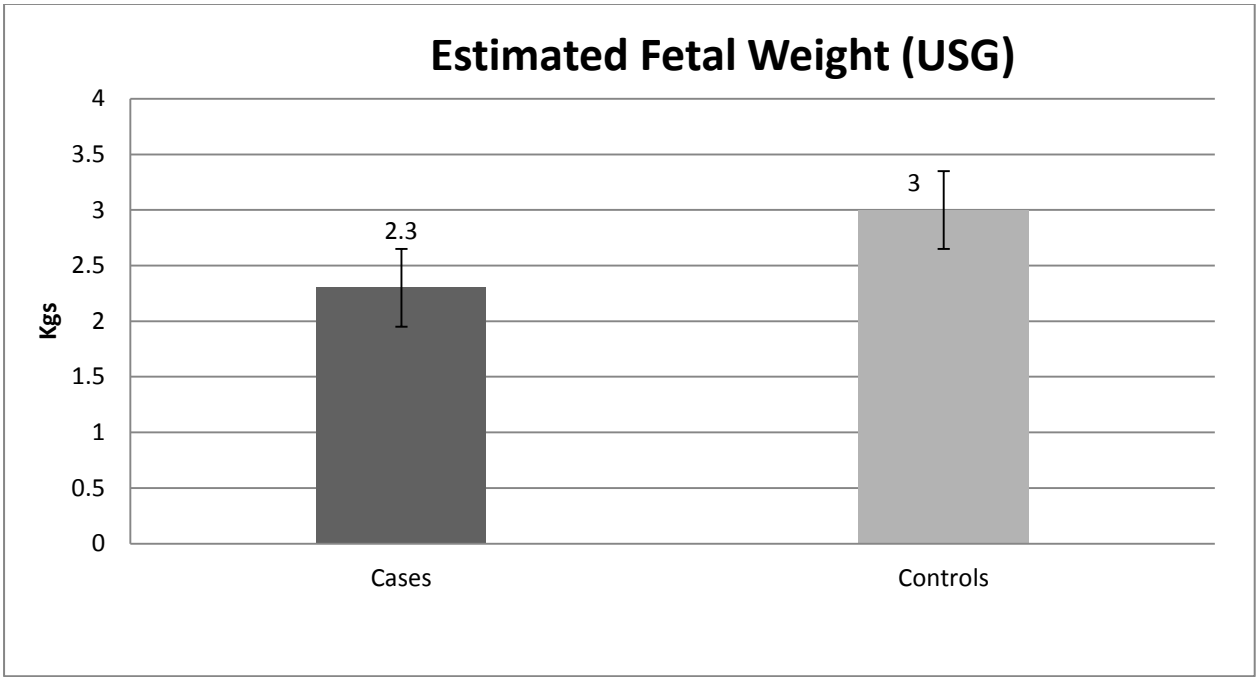


Graph 5: Bar diagram showing Mean Period of gestation between two groups by USG at term

Table 6: Estimated fetal weight by USG between two study groups

	Cases (n=40)		Controls (n=40)		p value
	Mean	SD	Mean	SD	
Estimated Fetal Weight by USG	2.3	0.3	3.0	0.3	<0.001*

Mean estimated fetal weight by USG in cases was 2.3 ± 0.3 Kgs and in controls it was 3.0 ± 0.3 Kgs. *There was significant difference statistically in estimated fetal weight between two groups.

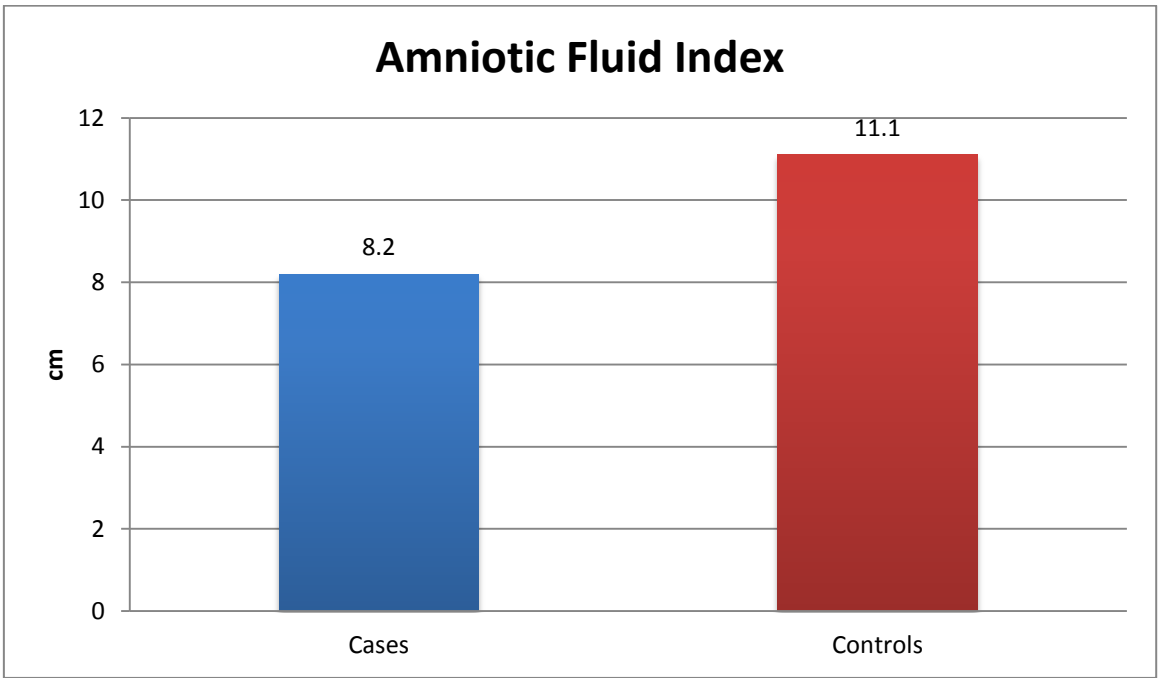


Graph 6: Bar diagram showing USG estimated fetal weight between two study groups

Table 7: Amniotic Fluid Index between two study groups

	Cases (n=40)		Controls (n=40)		p value
	Mean	SD	Mean	SD	
Amniotic Fluid Index	8.2	4.3	11.1	2.6	<0.001*

Mean Amniotic Fluid Index in cases was 8.2 ± 4.3 cm and in controls it was 11.1 ± 2.6 cm.
*There was significant difference statistically in Amniotic Fluid Index between two groups.

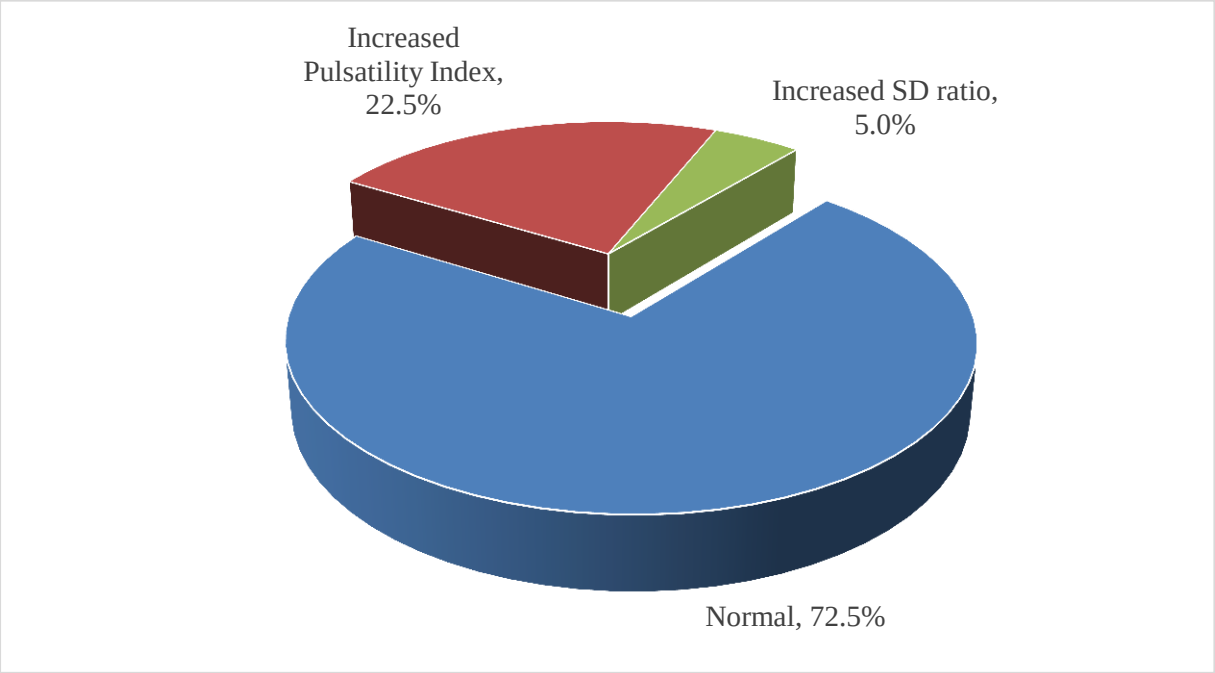


Graph 7: Bar diagram showing Amniotic Fluid Index between two study groups

Table 8: Umbilical Artery Doppler findings among Cases

		Cases (n=40)	
		Number	%
Umbilical Artery Doppler	Normal	29	72.5
	Increased Pulsatility Index	9	22.5
	Increased SD ratio	2	5

Among cases Umbilical artery Doppler was normal in 72.5%, Pulsatility Index was increased in 22.5% and SD ratio was increased in 5%.

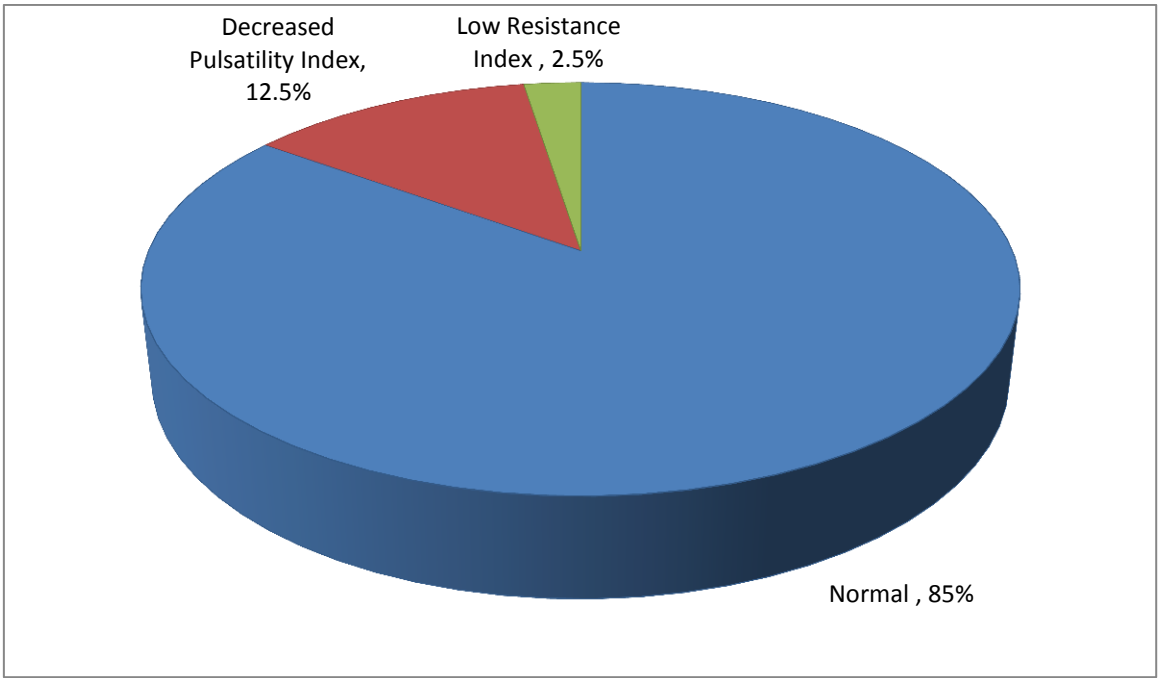


Graph 83: Pie diagram showing Umbilical artery Doppler findings in Cases

Table 9: Middle cerebral artery (MCA) Doppler findings among cases

		Cases (n=40)	
		Number	%
MCA	Normal	34	85
	Decreased Pulsatility Index	5	12.5
	Low Resistance Index	1	2.5

Among cases MCA Doppler was normal in 85%, Pulsatility Index was decreased in 12.5% and Resistance Index was low in 2.5%.

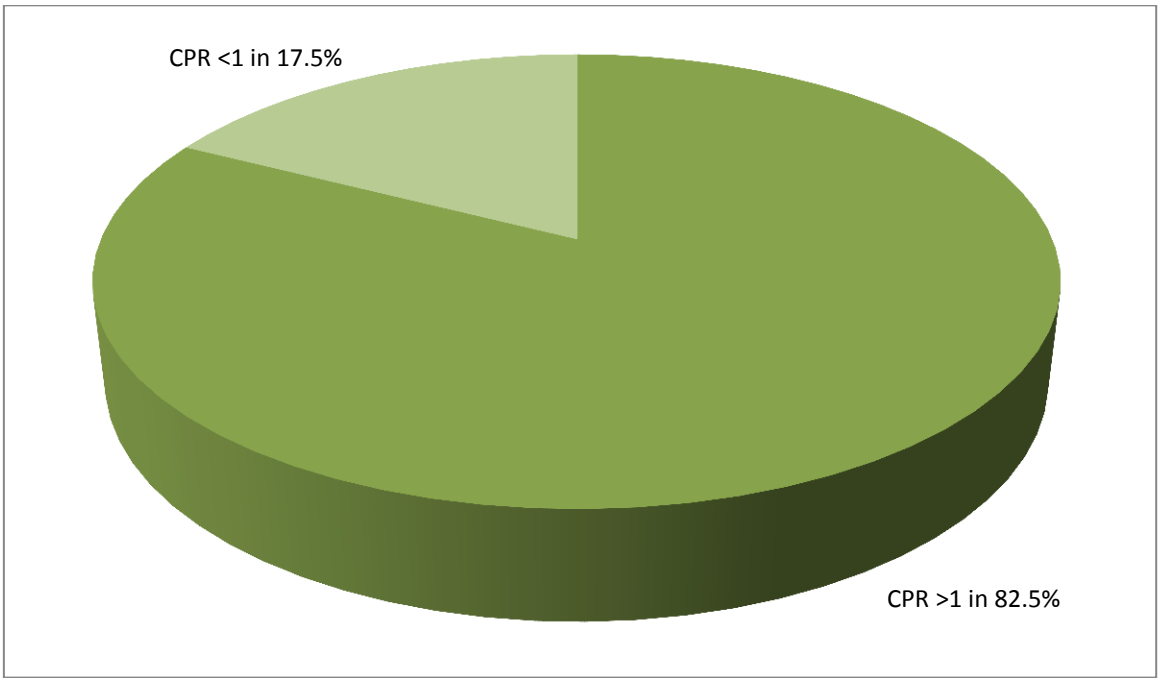


Graph 9: Pie diagram showing MCA Doppler findings among cases

Table 10: Cerebro Placental Ratio (CPR) among cases

	Cases (n=40)	
	Number	%
CPR <1	7	17.5
CPR >1	33	82.5

In cases CPR was <1 in 17.5% of subjects



Graph 10 : Pie diagram showing Cerebro Placental Ratio among cases

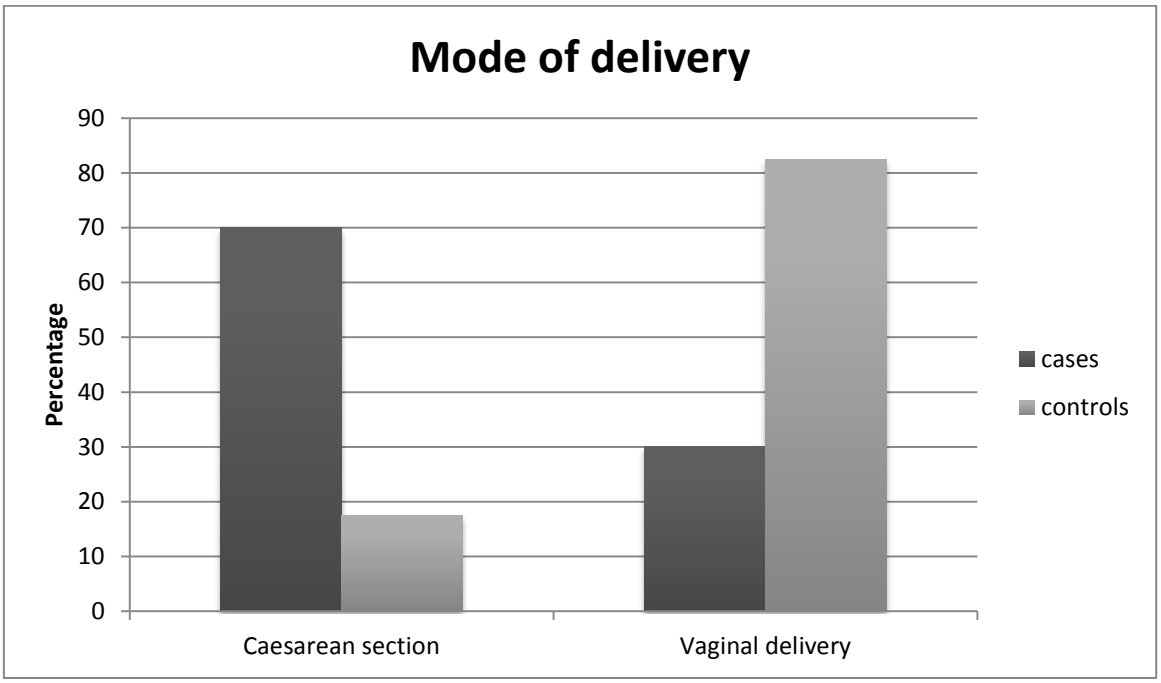
Table 11: Comparison of Mode of delivery between two study groups

		Cases (n=40)		Controls (n=40)	
		Number	%	Number	%
Mode of Delivery	Caesarean section	28	70	7	17.5
	Vaginal delivery	12	30	33	82.5

$\chi 2 = 22.4$, df = 1, p <0.001*

In cases (n=40), 70% delivered by caesarean section and 30% delivered vaginally. In controls (n=40), 17.5% delivered by caesarean section and 82.5% delivered vaginally.

*This difference in mode of delivery was statistically significant.



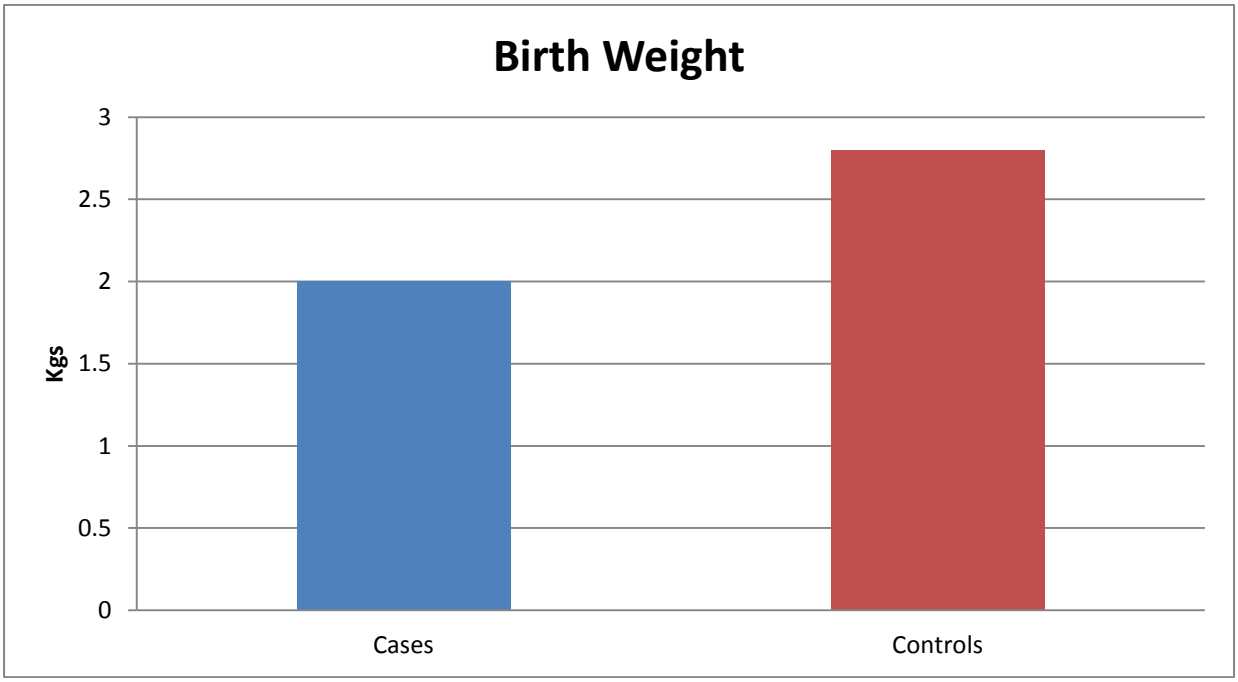
Graph 11: Bar diagram showing Mode of delivery comparison between two study groups

Table 12: Comparison of Birth weight between two study groups

	Cases (n=40)		Controls (n=40)		p value
	Mean	SD	Mean	SD	
Birth Weight	2.0	0.3	2.8	0.3	<0.001*

Mean birth weight of babies in cases was 2 ± 0.3 Kgs and in controls it was 2.8 ± 0.3 Kgs.

* This difference in mean birth weight was statistically significant.

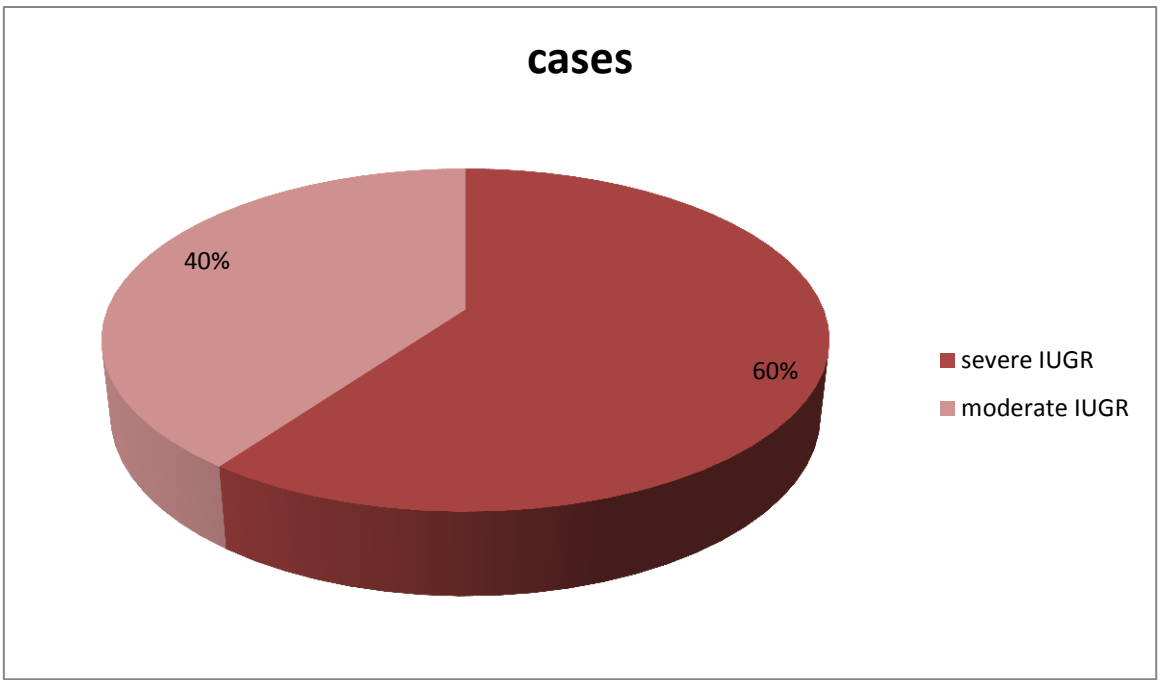


Graph 12: Bar diagram showing Birth weight comparison between two study groups

Table 13: Grading of IUGR based on birth weight

		Cases (n=40)	
		Number	%
Birth Weight	<3rd Percentile	24	60
	3rd to 10th Percentile	16	40

In the study among cases 60% had birth weight <3rd Percentile, 40% had birth weight between 3rd to 10th percentile. <3rd Percentile signifies severe IUGR, 3rd to 10th percentile signifies moderate IUGR.

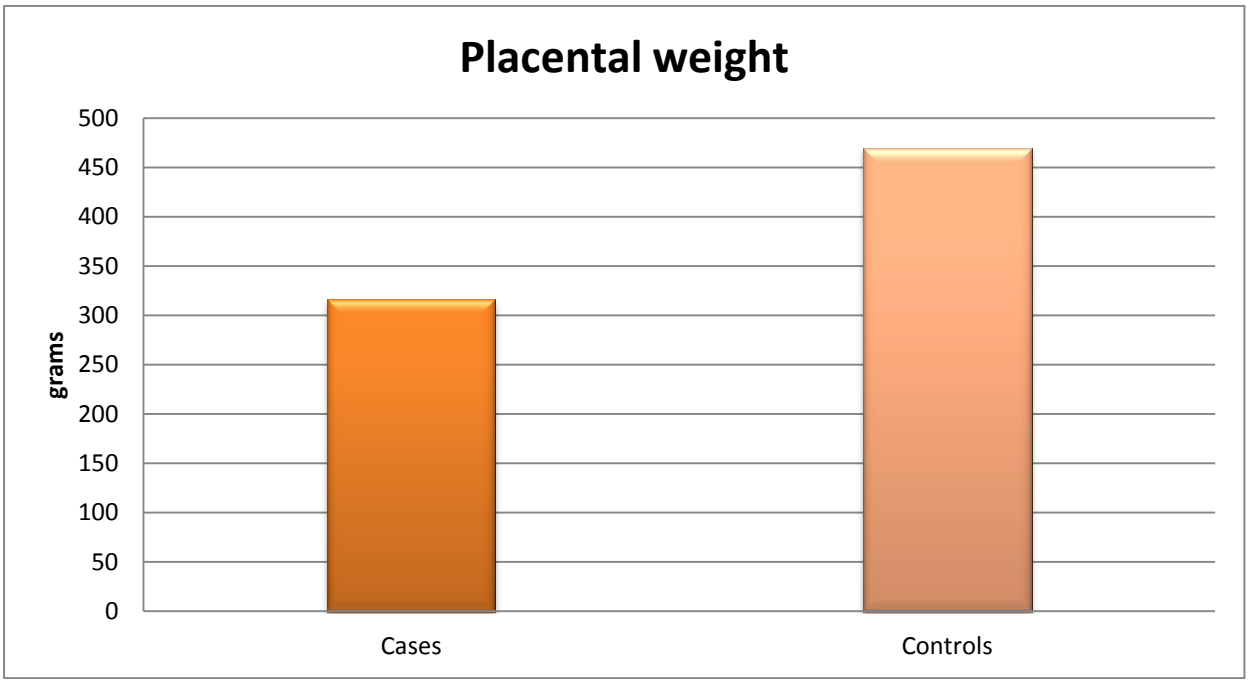


Graph 13: Pie diagram showing grading of IUGR based on birth weight

Table 14: Comparison of placental weight between two study groups

	Cases (n=40)		Controls (n=40)		p value
	Mean	SD	Mean	SD	
Placenta Weight in grams	316.3	62.5	470	79.7	<0.001*

Mean placental weight in cases was 316.3 ± 62.5 gms and in controls it was 470 ± 79.7 gms. This difference in mean placental weight between two groups is statistically significant*



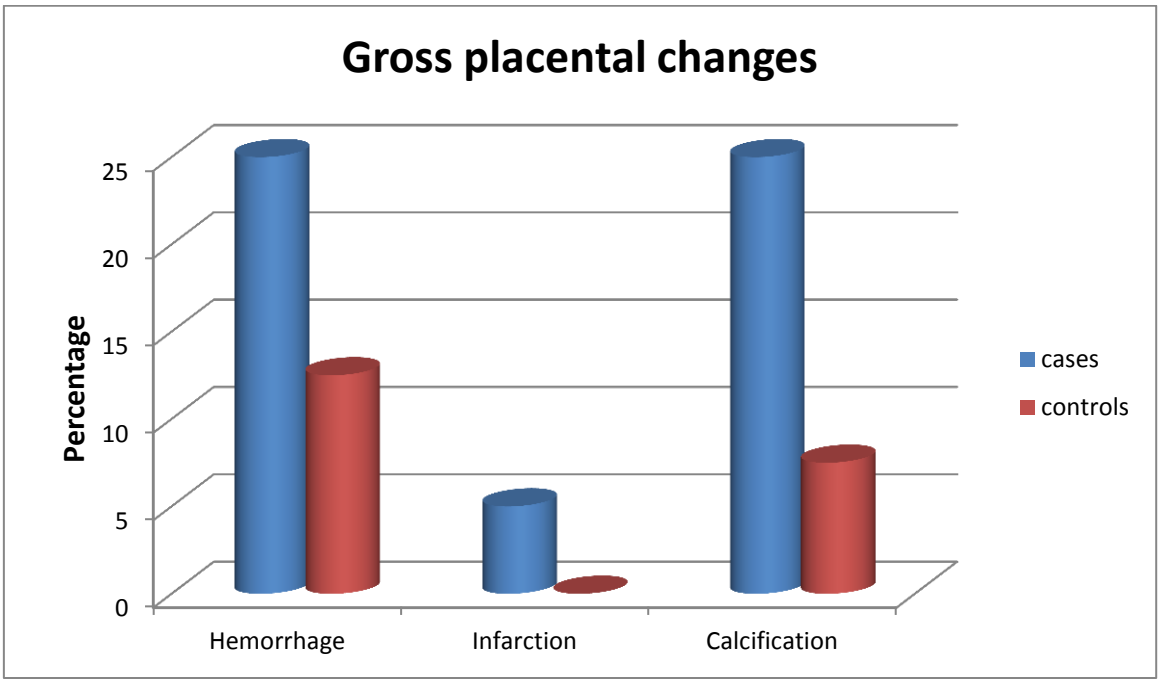
Graph 14: Bar diagram showing Placental Weight Comparison between two study groups

Table 15: Comparison of Gross changes of placenta between two study groups

Gross Placental changes	Cases (n=40)		Controls (n=40)		p value
	Number	%	Number	%	
Hemorrhage	10	25	5	12.5	0.152
Infarction	2	5	0	0	0.152
Calcification	10	25	3	7.5	0.03*

Hemorrhage was seen in 25% of cases and 12.5% of controls. Infarction was see in 5% of cases and none in controls. Calcification was seen in 25% of cases and 7.5% of controls.

*Statistically significant difference was observed in calcification (p value 0.03) between two groups.



Graph 15: Bar diagram showing comparison of Gross placental changes between two study groups

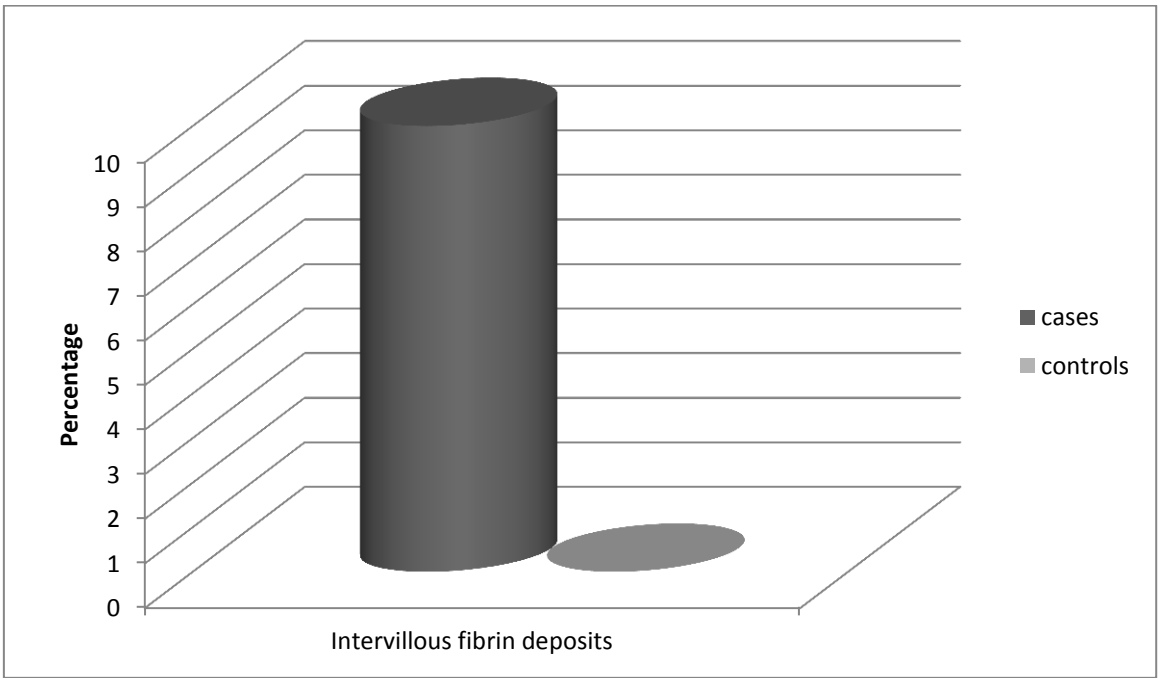
Table 16: Comparison of Intervillous Fibrin Deposits between cases and controls

		Cases (n=40)		Controls (n=40)	
		Number	%	Number	%
Intervillous Fibrin Deposits	Present	4	10	0	0
	Absent	36	90	40	100

p value 0.04*

10% of cases and none in controls showed Intervillous Fibrin Deposits

*Significant difference between cases and controls was observed for Intervillous Fibrin Deposits



Graph 16: Bar diagram showing Comparison of Intervillous fibrin deposits between two groups

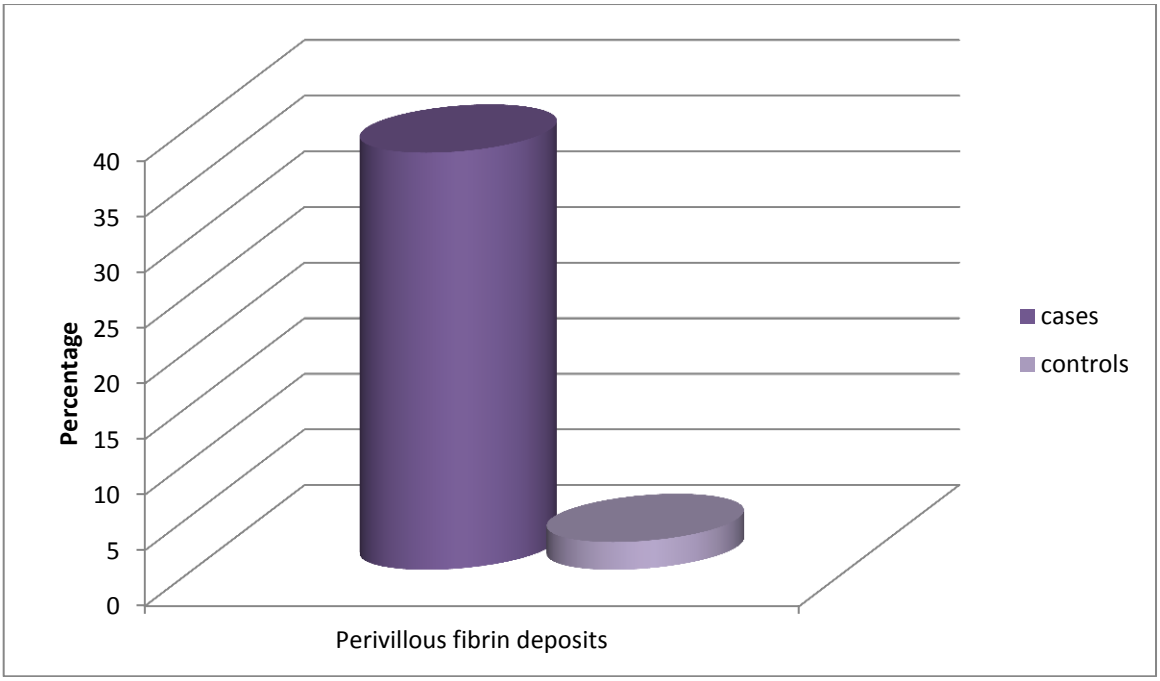
Table 17: Comparison of Peri villous fibrin deposits between cases and controls

		Cases (n=40)		Controls (n=40)	
		Number	%	Number	%
Peri Villous Fibrin Deposits	Present	15	37.5	1	2.5
	Absent	25	62.5	39	97.5

p value <0.001*

37.5% of cases and 2.5% of controls showed Peri Villous Fibrin Deposits

*Significant difference between cases and controls was observed for Peri villous Fibrin Deposits



Graph 17: Bar diagram showing Comparison of Peri villous fibrin deposits between two groups

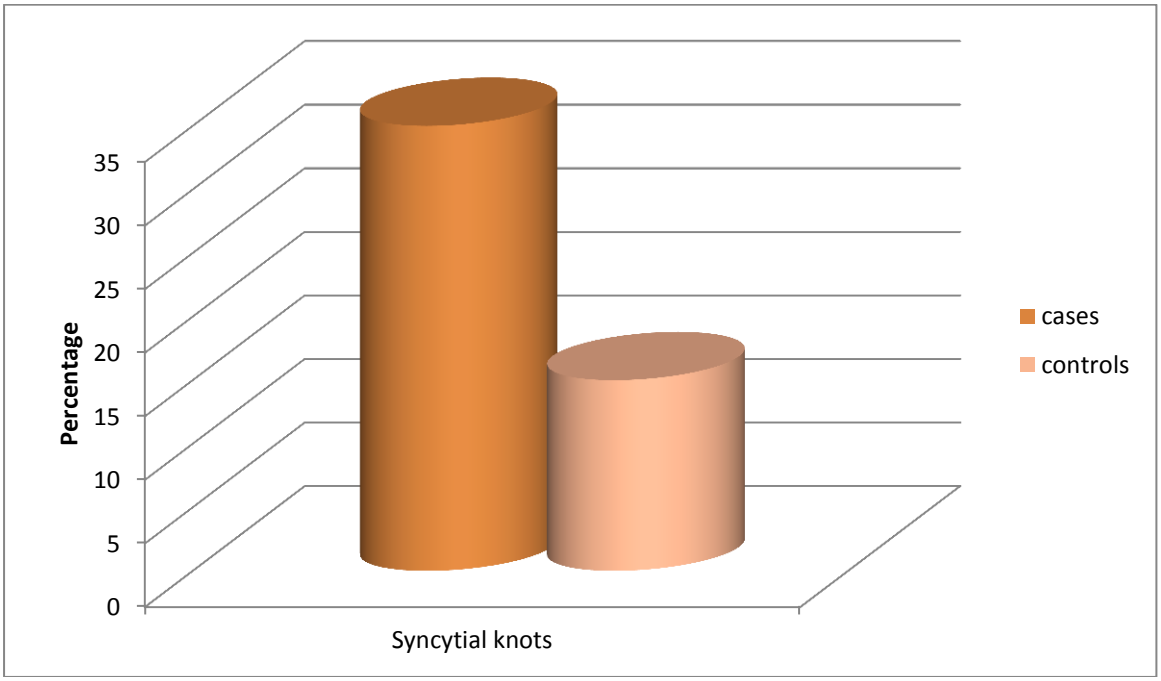
Table 18: Comparison of syncytial knots between cases and controls

		Cases (n=40)		Controls (n=40)	
		Number	%	Number	%
Syncytial Knots	Present	14	35	6	15
	Absent	26	65	34	85

p value 0.039*

35% of cases and 15% of controls had Syncytial knots

*Significant difference between cases and controls was observed for Syncytial Knots.



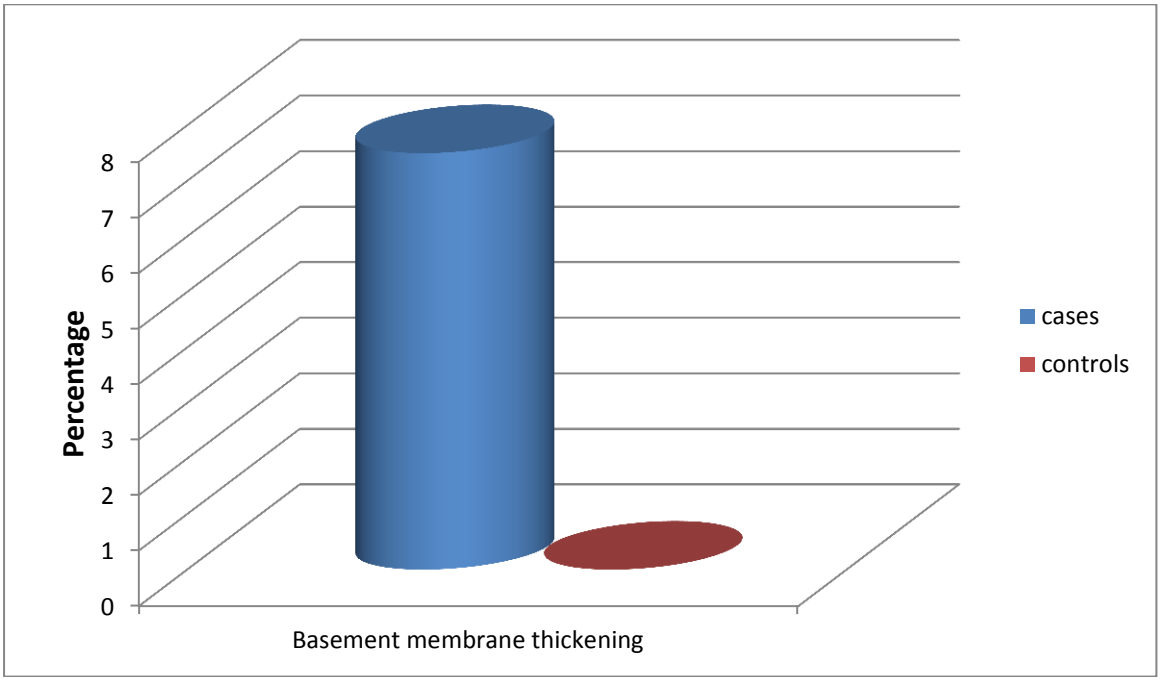
Graph 18: Bar diagram showing Comparison of Syncytial knots between two groups

Table 19: Comparison of Basement membrane thickening between cases and controls

		Cases (n=40)		Controls (n=40)	
		Number	%	Number	%
Basement Membrane Thickening	Present	3	7.5	0	0
	Absent	37	92.5	40	100

p value 0.077

7.5% of cases and none in controls had Basement Membrane Thickening



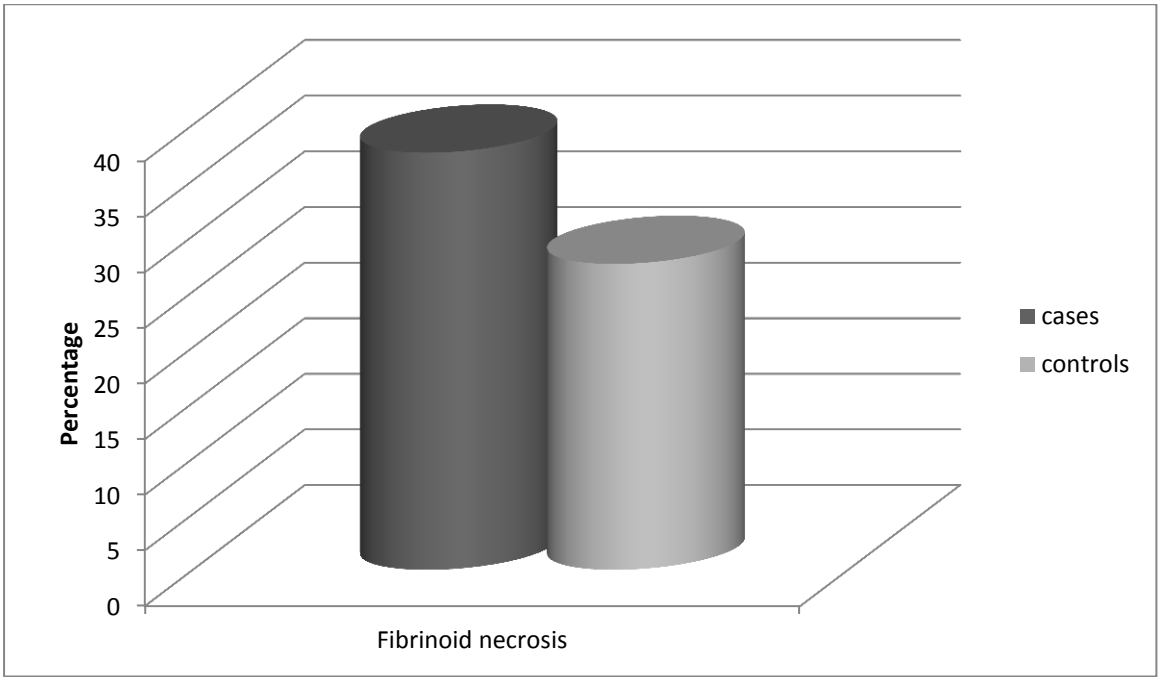
Graph 19: Bar diagram showing Comparison of Basement membrane thickening between two groups

Table 20: Comparison of Fibrinoid necrosis between cases and controls

		Cases (n=40)		Controls (n=40)	
		Number	%	Number	%
Fibrinoid Necrosis	Present	15	37.5	11	27.5
	Absent	25	62.5	29	72.5

p value 0.340

37.5% of cases and 27.5% of controls had Fibrinoid Necrosis



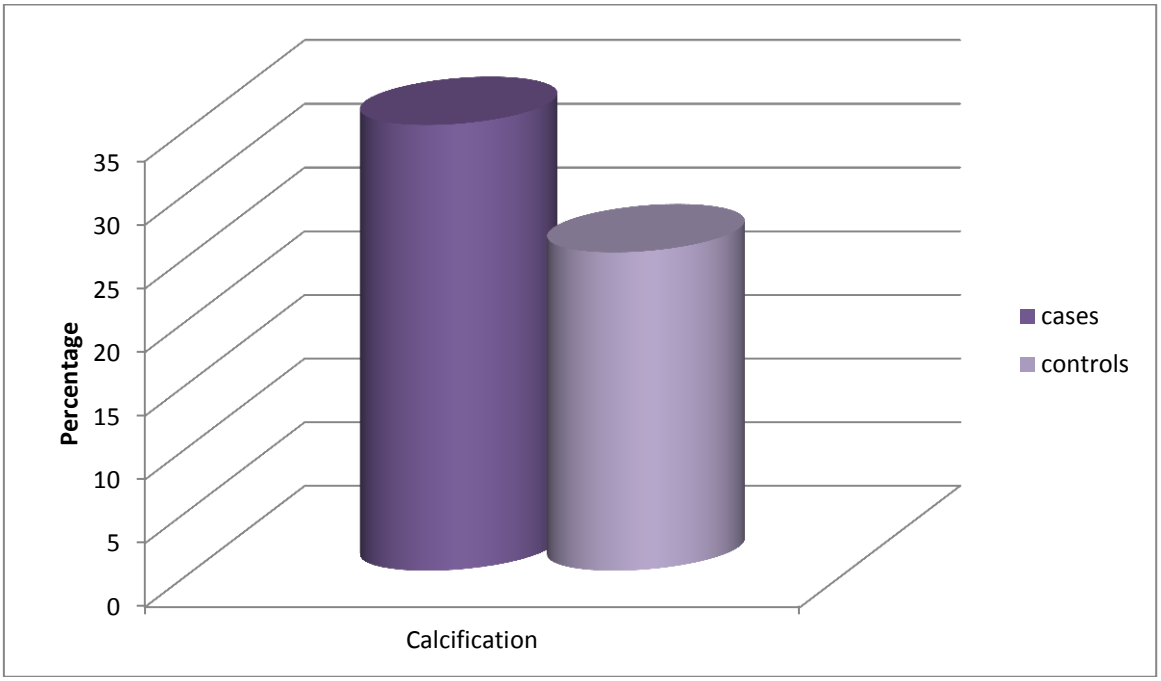
Graph 20: Bar diagram showing Comparison of Fibrinoid necrosis between two groups

Table 21: Comparison of Calcification between cases and controls

		Cases (n=40)		Controls (n=40)	
		Number	%	Number	%
Calcification	Present	14	35	10	25
	Absent	26	65	30	75

p value 0.329

35% of cases and 25% of controls had Calcification



Graph 21: Bar diagram showing Comparison of Calcification between two groups

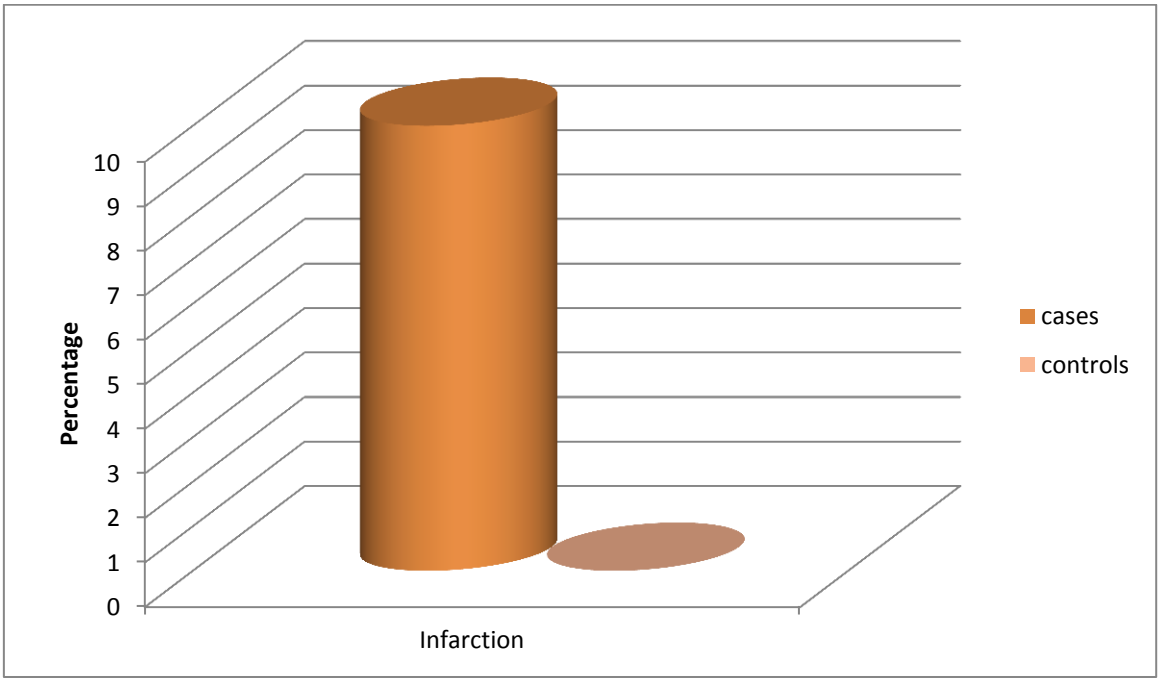
Table 22: Comparison of Infarction between cases and controls

		Cases (n=40)		Controls (n=40)	
		Number	%	Number	%
Infarction	Present	4	10	0	0
	Absent	36	90	40	100

p value 0.040*

10% of cases and none in controls had infarction

*Significant difference between cases and controls was observed for Infarction.



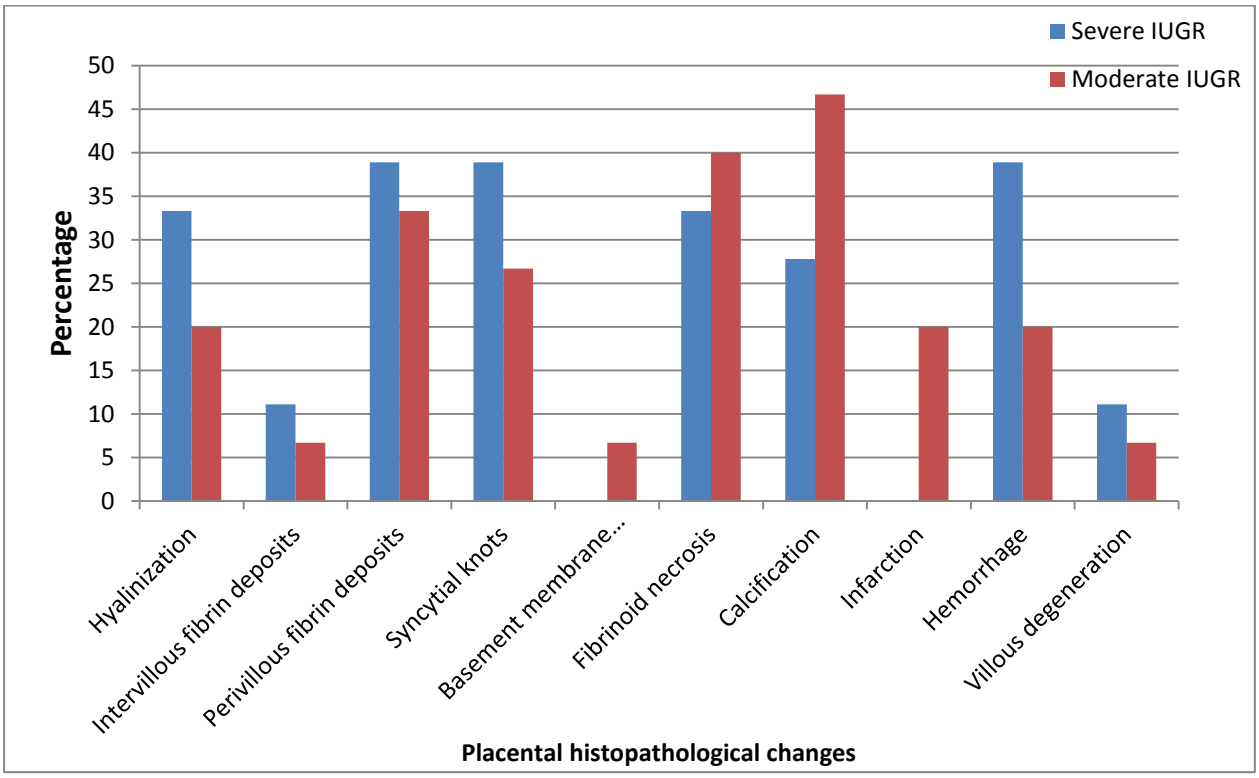
Graph 22: Bar diagram showing Comparison of Infarction between two groups

Table 23: Comparison of severity of IUGR with placental histopathological changes

Placental histopathological changes	Severe IUGR (n=18)		Moderate IUGR (n=15)		p value
	Number	%	Number	%	
Hyalinization	6	33.3	3	20	0.392
Intervillous Fibrin Deposits	2	11.1	1	6.7	0.658
Peri Villous Fibrin Deposits	7	38.9	5	33.3	0.741
Syncytial Knots	7	38.9	4	26.7	0.458
Basement Membrane Thickening	0	0	1	6.7	0.266
Fibrinoid Necrosis	6	33.3	6	40	0.692
Calcification	5	27.8	7	46.7	0.261
Infarction	0	0	3	20	**0.047***
Hemorrhage	7	38.9	3	20	0.240
Villous Degeneration	2	11.1	1	6.7	0.658

In the study among cases there was no significant difference in placental histopathological changes with respect to severity of IUGR, except for Infarction. 20% of moderate IUGR subjects had infarction.

*This difference was statistically significant.



Graph 23: Bar diagram showing Comparison of severity of IUGR with placental histopathological changes

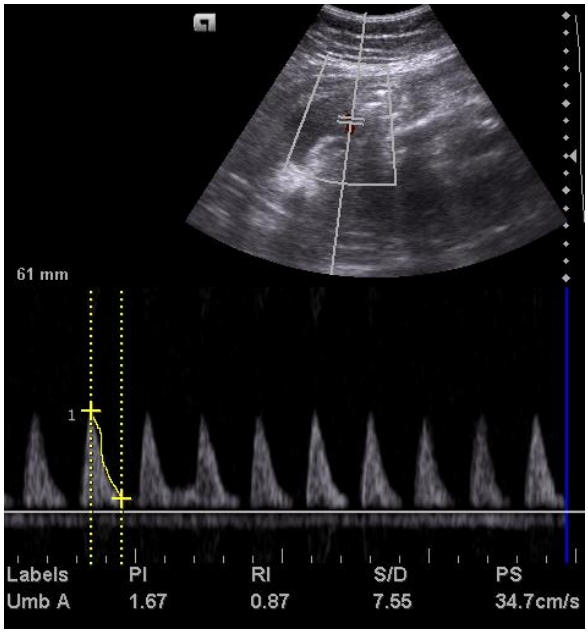


Figure 6 : Absent End Diastolic Flow In Umbilical Artery

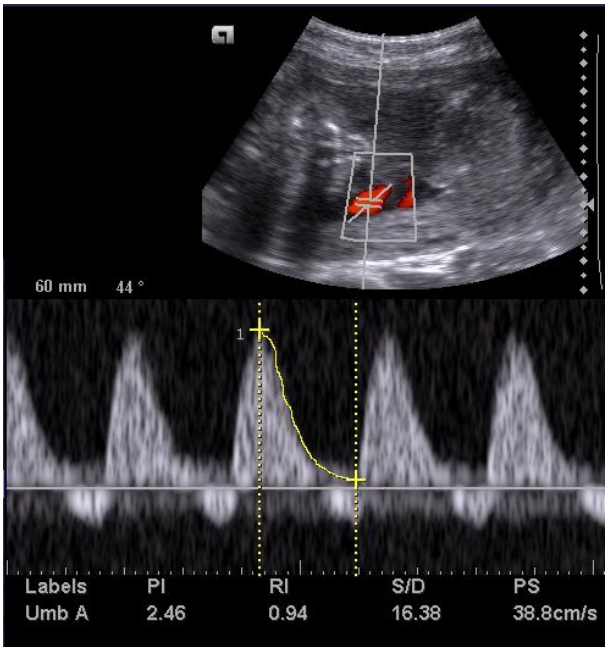


Figure 7 : Reversal Of Flow In Umbilical Artery

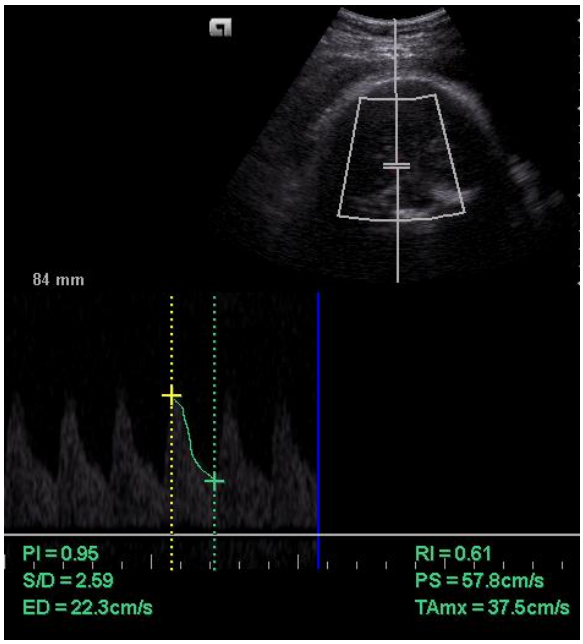


Figure 8 : Low PI and RI Of Middle Cerebral Artery

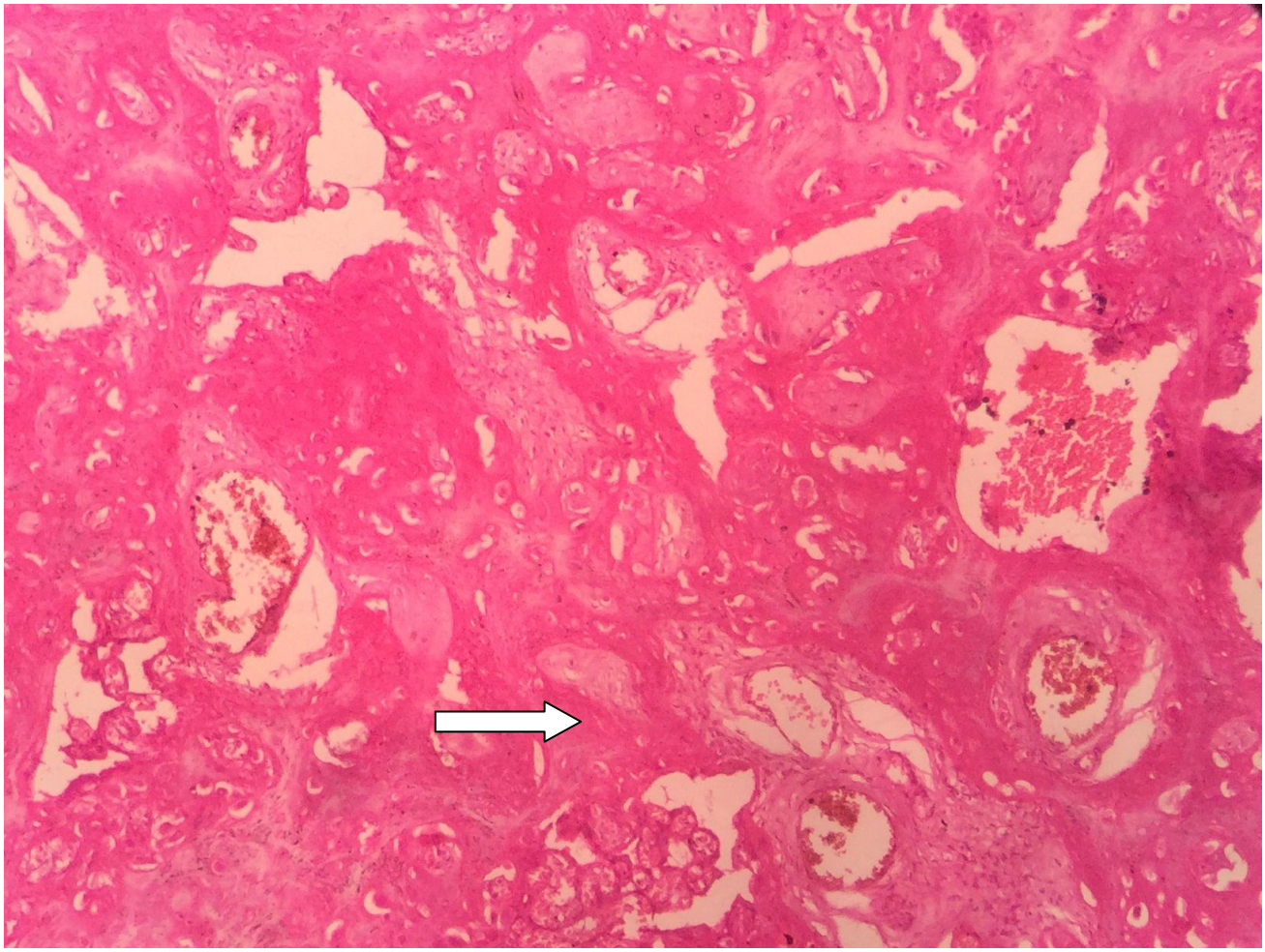


Figure 9 : Microphoto graph showing perivillous fibrin deposition (H&E, X100)

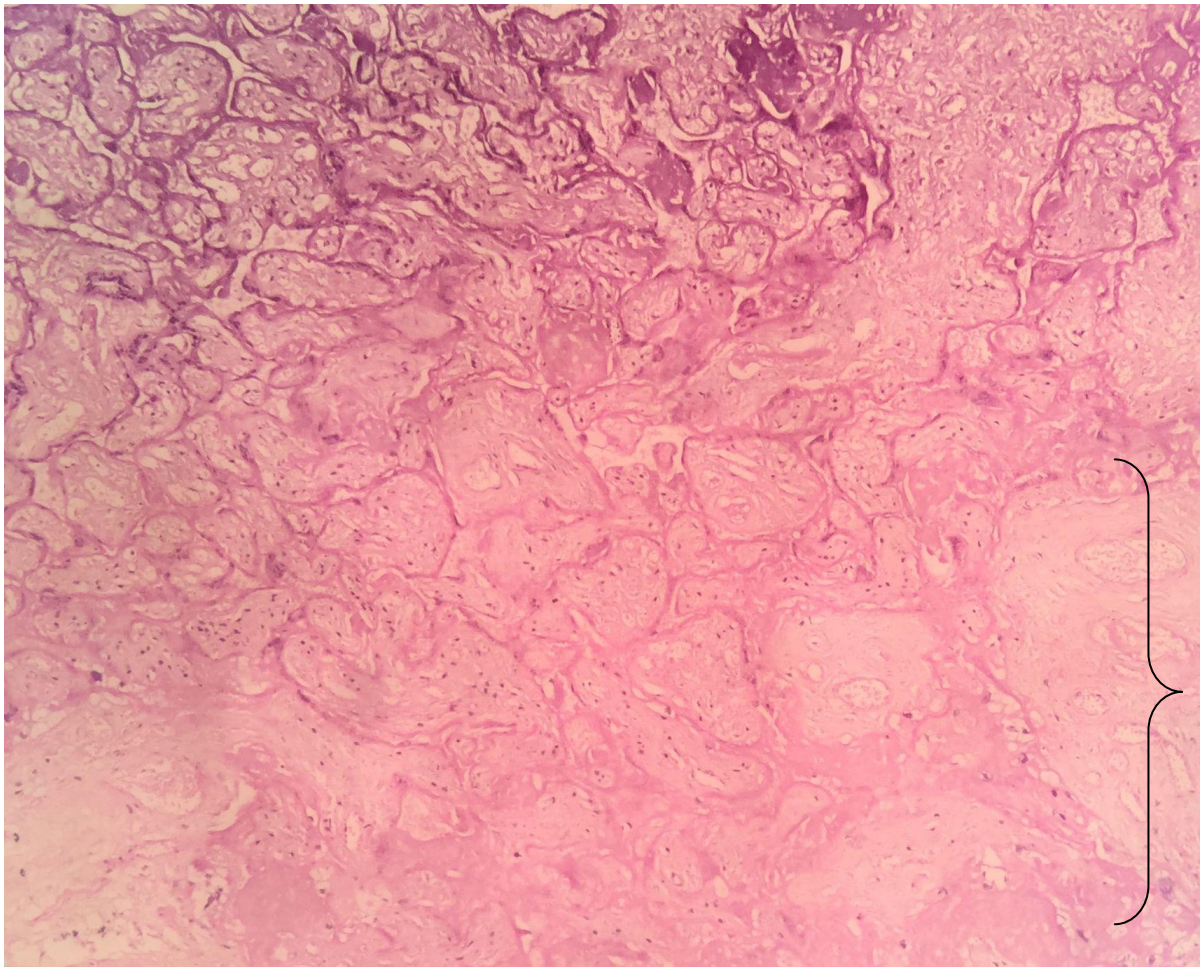


Figure 10 : Microphoto graph (lower half) showing placental infarction (H&E, X100)

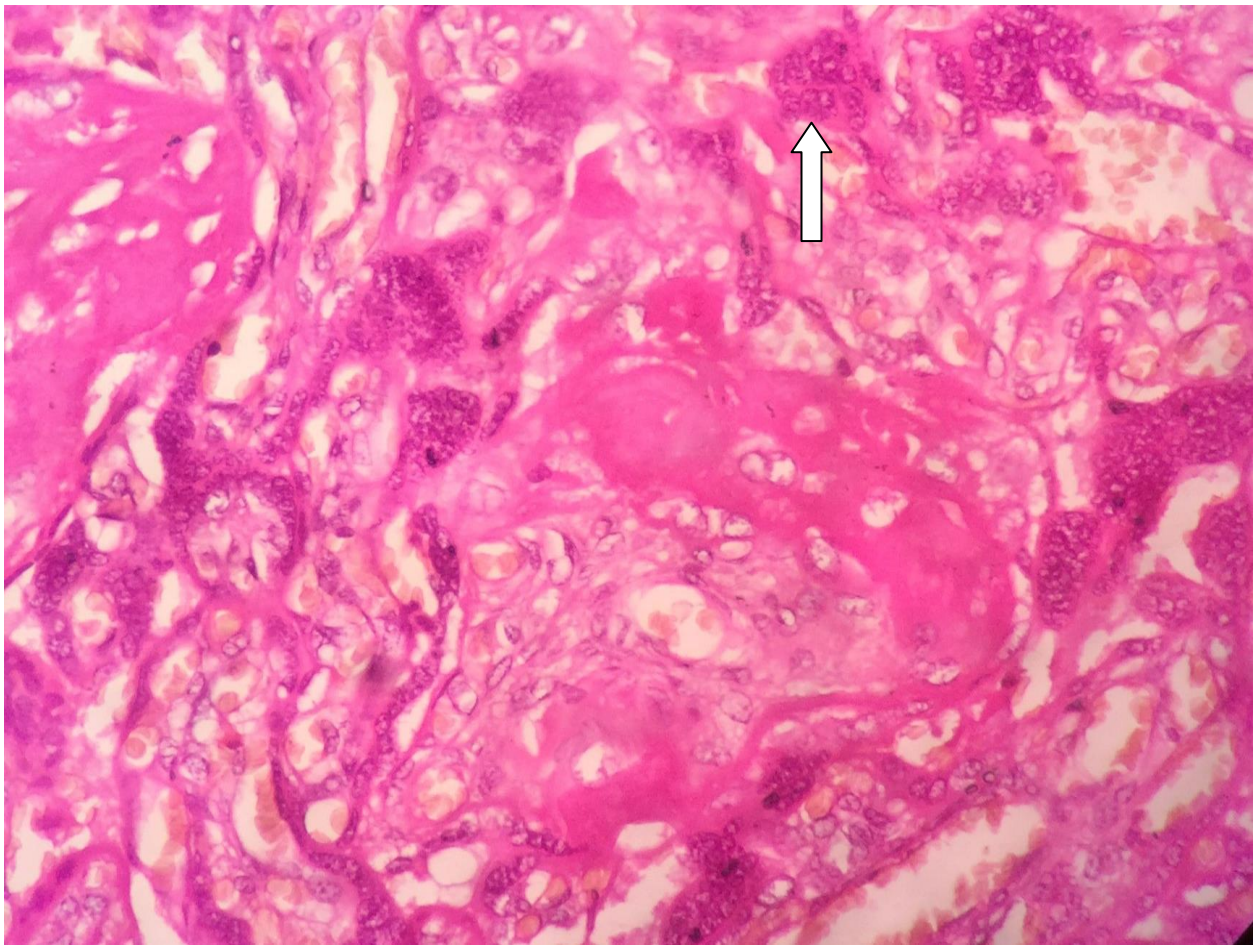


Figure 11 : Microphotograph showing Syncytial knots (H&E, X400)

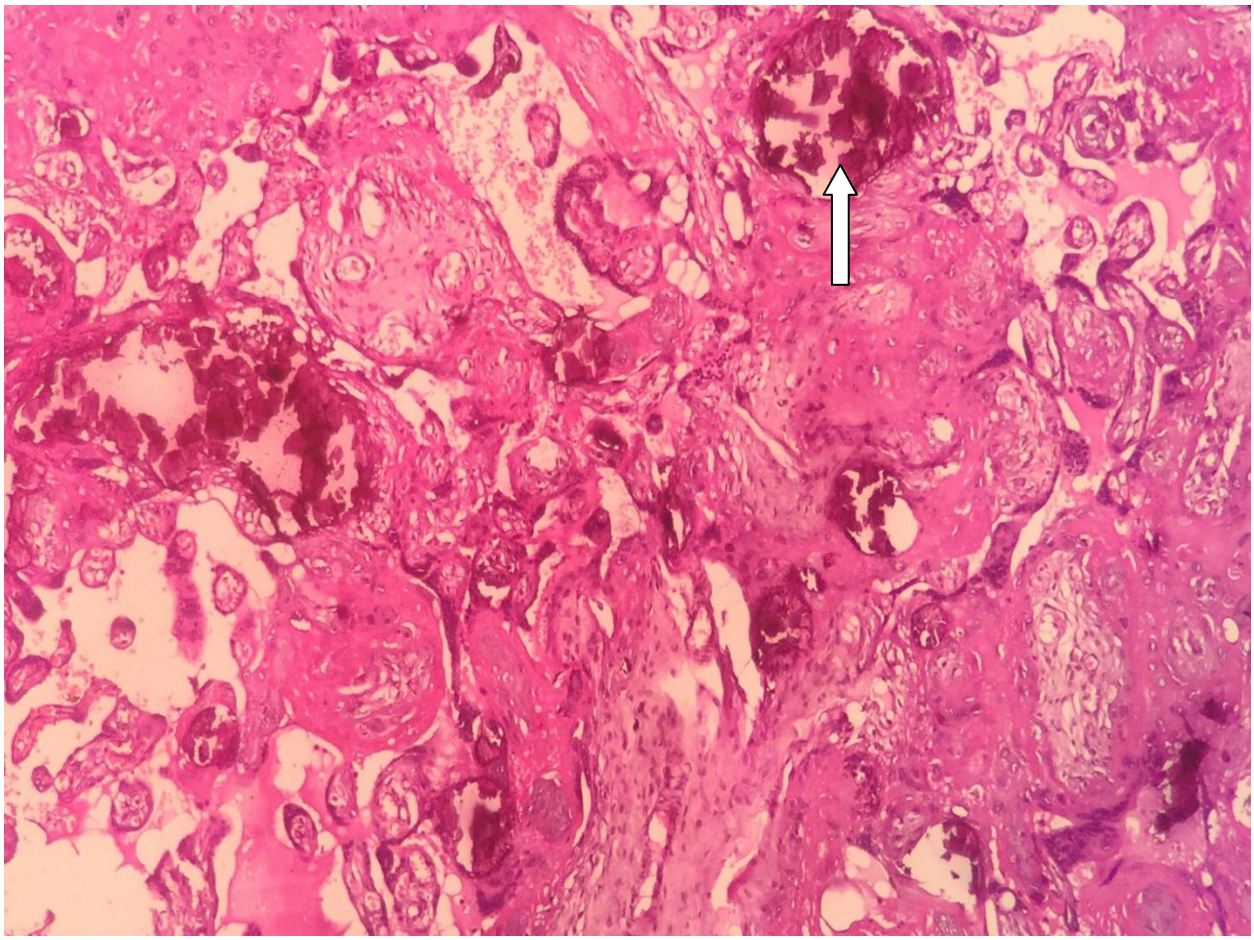


Figure 12 : Microphoto graph showing extensive calcification (H&E, X100)

DISCUSSION

As Intrauterine growth retardation (IUGR) constitutes an important clinical entity associated with high perinatal morbidity such as low birth weight, NICU admission and long term sequelae like risk of neurodevelopmental impairment and high risk of diabetes and cardiovascular disease in adulthood,[68] evaluation of placenta has become important to understand the pathophysiology of IUGR. The underlying causes and recurrence risks can be understood with careful examination of placenta along with clinico-pathologic correlation.[5]

It is assumed that most of the observed placental abnormalities are due to uteroplacental ischemia and the fetal vascular abnormalities are a reflection of the fetal growth retardation.[69]

The need to identify growth restricted fetuses in pregnancy is to improve perinatal outcomes through sonographic fetal surveillance and colour Doppler and hence to decide the optimal timing of delivery.[70]

In this study, Mean age of cases was 23.9 ± 4.2 years and controls was 23.7 ± 3.8 years. There was no significant difference in mean age between two groups.

There was no significant difference in parity between two groups which meant equal distribution was achieved with respect to parity. In our study all the subjects (both cases and controls) were term pregnancies. There was no significant difference with respect to maternal age and parity according to various studies done by Vedmedovska et al,[67] Parra-Saavedra et al,[71] O'Dwyer et al,[72] and Tomas SZ et al[73] similar to our study.

There was statistically significant difference ($p < 0.001$) between cases and controls in terms of clinically detectable growth lag on per abdomen examination. In cases, 45% had severe IUGR with 6weeks lag in fundal height, 37.5% had moderate IUGR with 4weeks lag in fundal height and 17.5% had fundal height appropriate for period of gestation. According to

Gardosi et al,[74] lag in fundal height of 4weeks is suggestive of moderate IUGR, while a lag of over 6weeks suggests severe IUGR. However, this method had low sensitivity(44%) when used alone.

RCOG[75] recommends that use of a customized fundal chart improves the accuracy of detecting IUGR and the sensitivity of detecting IUGR by fundal height ranges from 27% to 86% which supports our study. According to SOGC guidelines,[76] fundal height determination has limited value in routine obstetrical care, but serves to be the only physical examination screening test available.

It was observed that mean period of gestation by USG in cases was 34.6 ± 1.9 weeks and in controls it was 37.4 ± 1.5 weeks and there was significant difference statistically in POG between two groups ($p < 0.001$) in our study. Mean gestational age in weeks was 36.72 ± 1.68 weeks which was less compared to the controls according to study done by Majid et al.[77]

Mean estimated fetal weight by USG in cases was 2.3 ± 0.3 Kgs and in controls it was 3.0 ± 0.3 Kgs proving statistical significance with p value of <0.001. According to Saha et al,[78] IUGR fetuses had lower estimated fetal weight as compared to the controls which was similar to our study. Sonographically estimated fetal weight turned out to be the best parameter for diagnosing IUGR according to Craigo SD.[79] Due to limitations of detecting IUGR clinically, both ACOG[80] and RCOG[76] recommend biometric measurements of the fetus and EFW for detection of IUGR.

Significant difference ($p < 0.001$) was observed with respect to mean Amniotic Fluid Index between cases (8.2 ± 4.3cm) and controls (11.1 ± 2.6cm). Studies have shown that in IUGR fetuses, amniotic fluid index progressively decreases. According to Cosmi et al,[81] 20-30% of IUGR cases had oligohydramnios. Scifres et al[82] found that presence of oligohydramnios (amniotic fluid index < 5) was significant in IUGR and predicted perinatal mortality.

Interestingly, ACOG[80] considers amniotic fluid (AF) an "important and prognostic parameter in fetuses with IUGR," whereas RCOG[75] recommends that assessment of AF has "minimal value in diagnosing" inadequate growth.

Umbilical artery Doppler study in growth restricted fetal surveillance reduced the incidence of obstetric interventions like induction of labor and caesarean section.[83] In our study, among cases Umbilical artery Doppler was normal in 72.5%, PI was increased in 22.5% and SD ratio was increased in 5%. The national multicenter PORTO (Prospective Observational Trial to Optimize Pediatric Health)[32] study identified less adverse outcomes in FGR fetuses with normal Doppler than abnormal Doppler. According to the Irish guidelines,[84] abnormal umbilical artery Doppler significantly increases the risk of adverse perinatal outcome in growth restricted fetuses compared with normal umbilical artery Doppler. A recent Cochrane review, concluded that using umbilical artery Doppler reduced the risk of perinatal death by 29 to 38 percent.[30] Lindqvist and Molin[85] found that antenatal detection of IUGR by umbilical artery Doppler significantly improved perinatal outcome. A study conducted by Brodszki et al[86] concluded that Doppler examination of umbilical artery is considered a valuable parameter in clinical decision making.

Both ACOG[80] and RCOG[75] guidelines agree on the use of umbilical artery (UA) Doppler in the management of IUGR, although RCOG[75] emphasizes that it should be the primary surveillance tool and it can be used in predicting poor perinatal outcomes. For ACOG,[80] UA Doppler can be used to delay delivery with reassurance. Both national guidelines agree that absent or reversed UA Doppler is associated with poor perinatal outcome and high perinatal mortality.[75,80]

Middle cerebral artery Doppler velocimetry identifies IUGR fetuses at increased risk for cesarean delivery.[43] In our study, MCA Doppler was normal in 85%, PI was decreased in 12.5% and RI was low in 2.5% of subjects. In cases CPR was <1 in 17.5% of subjects. "Brain sparing" is seen on arterial Doppler ultrasound by increased impedance in the umbilical arteries and decreased impedance in the middle cerebral arteries.[87] As metabolic deterioration occurs and the fetus loses the ability to adapt to hypoxemia, there is an evident decreased resistance and increased diastolic flow in the cerebral circulation.[38,87] Long-term follow-up of IUGR fetuses with abnormal umbilical and middle cerebral arteries are at higher risk with poor neurodevelopmental outcome.[88]

Only current treatment for IUGR is delivery, with main consideration being appropriate timing based on the umbilical artery and middle cerebral artery Doppler flow velocimetry.[84] Majid et al,[77] concluded that ultrasound biometry combined with multi vessel Doppler ultrasound provides better evaluation of clinically suspected cases of intrauterine growth retardation as well as predicts severity of disease.

In the present study, difference between mean birth weight of babies in cases (2 ± 0.3 Kgs) and controls (2.8 ± 0.3 Kgs) proved statistical significance ($p < 0.001$).

Significant difference ($p < 0.001$) was observed between mean placental weight in cases (316.3 ± 62.5gms) and in controls (470 ± 79.7gms). According to a study done by Kotgirwar,[89] the mean fetal and placental weight in IUGR cases were reduced significantly compared to that of controls. Similar findings were reported by Vedmedovska et al,[63] Mallik G et al,[90] Althshuler G et al,[91] Mirchandani J et al,[92] Bhatia A et al[93] and Fox H.[94] According to Biswas et al,[18] Fox H,[95] and Oliveira et al,[96] placental and fetal weight were significantly lower in cases than in controls.

In our study among cases 60% had birth weight <3rd Percentile, 40% had birth weight between 3rd to 10th percentile. <3rd Percentile signifies severe IUGR, 3rd to 10th percentile signifies moderate IUGR. This difference in birth weight between two groups was statistically significant (p <0.001).

In the present study, statistically significant difference in gross placental changes was observed in calcification (p value 0.03) between two groups. According to Kotgirwar,[89] presence of calcification in cases (60%) was slightly more than controls (56%).

Many studies have reported variable prevalence of calcification from 8% to 100%. This may be due to the wide range in the number of cases included in various studies.

Table 24 : Comparison of calcification between various studies

Study	Percentage of calcification
Bhatia et al[93]	100%
Kotgirwar[89]	60%
Mirchandani et al[92]	29%
Our study	35%

Perivillous fibrin deposition is defined as the presence of a dense meshwork of fibres measuring <10mm in thickness with cross-striation of fibrin filaments with 20nm periodicity

and results from thrombosis of maternal blood.[97] The villi embedded in this fibrin are incapable of participating in transport of nutrients.[89]

This study reported statistically significant p value (<0.001) between cases (37.5%) and controls (2.5%) in terms of perivillous fibrin deposition. Mallik et al[90] and Mirchandani et al,[92] reported higher incidence of perivillous fibrin deposition of 36% and 21% respectively in their studies. According to Kotgirwar et al,[89] perivillous fibrin deposition was more in cases (16.7%) than controls (1.8%). Katzman PJ and Genest DR[98] observed that massive perivillous fibrin deposition was more common and strongly associated with IUGR than normal placenta.

Table 25 : Comparison of Perivillous fibrin deposits between various studies

Study	Percentage of perivillous fibrin deposits
Kotgirwar et al,[89]	16.7%
Mirchandani et al[92]	21%
Mallik et al[90]	36%
Katzman et al[98]	37.5%
Our study	37.5%

Our study showed significant difference in perivillous fibrin deposition between cases and controls similar to the above mentioned studies. Also our study showed significantly increased intervillous fibrin deposition similar to study done by Mardi K et al.[99]

Syncytial knots occur due to reduced perfusion of villi and its presence indicate decreased uteroplacental blood flow and hence functional inactivity.[89] According to Burton et al,[100] abnormal vascular remodeling and production of increased syncytial knots may be due to generation of reactive oxygen species under oxidative stress similar to a study done by Heazell and Moll.[36] Sankar KD et al,[101] in their study reported similar findings with the oxidative stress injury disrupting syncytiotrophoblast arrangement and resulting in increased vasculosyncytial membrane thickness and syncytial knot density. Heazell et al,[102] quantified syncytial knots as the number of syncytial knots per villous area. Fox[103] expressed syncytial knots based on total trophoblast volume. Mayhew et al,[104] calculated the percentage of terminal villi containing syncytial knots. Our study reported statistically significant p value (0.039) between cases (35%) and controls (15%) in terms of syncytial knots. According to Kotgirwar et al,[89] incidence of syncytial knots was higher in IUGR cases (60%) compared to control group. Mardi K et al,[90] suggested significant increase in syncytial knots in IUGR cases (38%) compared to controls.

Placental infarction is mainly due to loss of maternal blood supply

Placental infarction has been reported occasionally ranging from 0-10% by various studies.[90,92]

Heazell AE and Martindale EA[102] suggested that placental infarction was associated with clinical causes of still birth and IUGR. Burke C and Globe G[105] suggested that apoptosis was strongly associated with IUGR and placental infarction. According to study done by Kotgirwar et al,[89] placental infarction had a very low incidence (1.8%) compared to other findings. Vedmedovska[63] and Park et al,[106] reported higher incidence of villous infarction in IUGR pregnancies compared to normal pregnancies similar to study done by Mardi K et al.[90]

In the present study, statistically significant difference was observed in infarction (p value 0.040) between two groups. Also infarction was present in 20% of moderate IUGR category with significant p value of 0.047.

Our study showed significantly increased placental histopathological changes like intervillous fibrin deposits, perivillous fibrin deposits, syncytial knots, infarction and calcification in idiopathic term IUGR pregnancies as compared to that of normal pregnancies. These findings signify the predominant role of placental causes in idiopathic intrauterine growth restriction and pointed towards reduced blood flow to the placenta resulting in chronic placental insufficiency.

Umbilical artery and middle cerebral artery Doppler may improve obstetric outcome by providing appropriate timing for delivery and hence may reduce perinatal morbidity and mortality.

Therefore examination of placenta along with clinical detection of IUGR and Doppler velocimetry play an important role in the management of present pregnancy as well as prevention of IUGR in future pregnancies.

According to SOGC recommendations,[76] Low-dose aspirin should be prescribed to women with a previous history of intrauterine growth restriction. It should be initiated between 12 and 16 weeks' gestation and continued until 36 weeks.

Though large randomized control trial concluded low-dose aspirin has no benefit to prevent IUGR, meta-analysis of several earlier trials of smaller focused studies indicated some benefit.

CONCLUSION

In our study, clinical parameters such as fundal height, birth weight, placental weight were significantly decreased in idiopathic term IUGR pregnancies as compared to normal term pregnancies.

USG parameters like estimated fetal weight, mean gestational age and amniotic fluid index were reduced in idiopathic term IUGR pregnancies when compared with normal term pregnancies.

The histopathological changes of the placenta showed intervillous fibrin deposits, perivillous fibrin deposits, syncytial knots and infarction which turned out to be of significance in IUGR cases.

Umbilical artery and middle cerebral artery Doppler may improve obstetric outcome and reduce perinatal morbidity and mortality by providing appropriate timing for delivery.

To conclude, study of the placenta is an useful adjunct to the clinical examination in finding pathogenetic mechanisms resulting in IUGR pregnancies and can be helpful in the planning and management of future pregnancies with ultrasound and colour Doppler study.

SUMMARY

- All pregnant women with completed 37 to 42 weeks of gestation were included in the study.
- Those women fulfilling the inclusion criteria were included in the study group and women with term normal pregnancies were included as controls.
- 40 women were included in cases group and 40 women in control group.
- There was significant difference with respect to Mean Amniotic Fluid Index between cases (8.2 ± 4.3cm) and controls (11.1 ± 2.6 cm).
- Mean estimated fetal weight by USG between cases (2.3 ± 0.3 Kgs) and controls (3.0 ± 0.3 Kgs) was significant statistically ($p<0.001$).
- There was significant difference statistically between two groups ($p<0.001$) in terms of Mean period of gestation by USG in cases (34.6 ± 1.9 weeks) and in controls (37.4 ± 1.5 weeks).
- Umbilical artery PI was increased in 9 cases (22.5%) and SD ratio was increased in 2 cases (5%). Middle cerebral artery PI was decreased in 5 cases (12.5%) and RI was decreased in 1 case (2.5%). Cerebroplacental ratio was <1 in 7 cases (17.5%).
- There was significant statistical difference in Mean birth weight of babies between cases (2 ± 0.3 Kgs) and controls (2.8 ± 0.3 Kgs).
- All the gross and microscopic changes in the placentas of IUGR pregnancies were studied and compared with that of controls.

- Significant statistical difference was seen in Mean placental weight between cases (316.3 ± 62.5 gms) and controls (470 ± 79.7 gms).
- Gross placental changes like hemorrhage (25% vs 12.5%), infarction (5% vs 0%) and calcification (25% vs 7.5%) were noted more in cases compared to controls of which significant statistical difference was seen in calcification.
- Perivillous fibrin deposition was seen in 37.5% of cases and 2.5% of controls with significant p value of <0.001.
- Syncytial knots was higher in cases (35%) than in controls (15%) with significant difference (p value 0.039).
- Placental infarction was seen in 10% of the cases (p value 0.040).
- Other changes noted in placenta of idiopathic term IUGR pregnancies were – hyalinization, basement membrane thickening, fibrinoid necrosis, calcification, hemorrhage, villous degeneration.

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CASE PROFORMA

NAME: **AGE:** **IP NO:**
DOA: **Time of admission:** **DOD:**

OCCUPATION:
ADDRESS:
PHONE NUMBER:

H/O presenting complaints:

Obstetric history: Married life:
Consanguinous / Nonconsanguinous:
Gravid: Para: Living: Abortions: Dead:

Previous pregnancy details:

Present pregnancy details:

Menstrual history: Age of menarche:
Previous menstrual cycles:

LMP: EDD: POG:
POG acc. to wks scan:

Past history:
Family history:
Personal history: Diet: Appetite:
Sleep: Bowel/Bladder habits:
Addiction:

General physical examination :
weight : height:

Pallor :
Icterus:
Edema:
Clubbing/ Cyanosis/ Lymphadenopathy
Breast:
Thyroid:
Spine:

Vital signs: Temperature:
Pulse rate:
Respiratory rate:
Blood pressure:

Systemic examination
RS:
CNS:
CVS:

Per abdomen:
Uterus size:
Relaxed / Irritable / Acting
Presentation: cephalic/ others
FHS:

Per speculum:

Per vagina:

INVESTIGATIONS:

- Blood group and Rh typing:
- CBC
- RBS:
- HIV, HBsAG, VDRL:
- Urine routine and microscopy

- OBSTETRIC SCAN:

- FETAL DOPPLER:

DIAGNOSIS:

DETAILS OF DELIVERY:

Mode of delivery: Vaginal delivery/ Caesarean section

DETAILS OF NEONATE:

Sex : Male/Female Date:
Time:
Birth weight :
APGAR : 1'- 5'-
Admission to NICU:

PLACENTAL HISTOPATHOLOGY (PROFORMA)

- Gross weight
- Gross features : Hemorrhage, thrombosis, infarction, calcification
- Microscopic features : Infarction, hemorrhage, vasculitis, thrombosis, perivillous fibrin deposition, syncytial knots

INFORMED CONSENT

- STUDY TITLE: A STUDY OF PLACENTAL HISTOPATHOLOGICAL CHANGES IN IDIOPATHIC TERM IUGR PREGNANCIES

- INVESTIGATOR: Dr.Arulselvi.K
  Under the guidance of Dr. Munikrishna. M

- ADDRESS : Department of OBG,
  Sri Devaraj Urs Medical College, Kolar

- PLACE OF STUDY : R.L. Jalappa Hospital and Research Centre, attached to Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar,

Patient Information:

- We are doing this study to find out the cause for Idiopathic term IUGR pregnancies by studying the histopathological changes in placentae and comparing with the normal term pregnancies

- We will be taking the placenta after the delivery and sending for histopathological examination. If you agree to participate in this research study, the information will be kept confidential. You will not have to incur any additional expenditure. We will publish the results without revealing your name and identity. If you are not willing to participate in this research, it will not affect your treatment.

I_____ Participant hereby give consent to participate in the study mentioned above.

I have been explained that:

1) I understand the need to provide the placenta for the study
2) The data generated from my clinical examination and laboratory tests and other reports will be used in the study (which may be substantially published or used for further research) without revealing my identity in any manner.
3) I do not suffer any adverse health consequences by my participation in the study.
4) I am free to withdraw from the study anytime.

- I affirm that I have been given full information about the purpose of the study and the procedure involved and have been given ample opportunity to clarify my doubts. In giving my consent, I have not faced any trouble. I have been informed that not withstanding this consent given, I can withdraw from the study at any stage.

Signature of participant	Signature of witness
Name of participant	Name of witness

KEYS TO MASTER CHART

POG – Period of gestation

USG POG – Period of gestation by ultrasonography

USG EFW – Estimated fetal weight by ultrasonography

AFI – Amniotic fluid index

Umb A – Umbilical artery

MCA – middle cerebral artery

CPR – cerebroplacental ratio

Hem – hemorrhage

Inf – infarction

Cal – calcification

Hya – hyalinization

IVF – intervillous fibrin deposits

PVF – perivillous fibrin deposits

Syn – syncytial knots

BM – basement membrane thickening

Fib Nec – fibrinoid necrosis

Vil Deg – villous degeneration

PI – pulsatility index

SD – systolic diastolic ratio

RI – resistance index

CS – caesarean delivery

VD – vaginal delivery

n - normal

N – No/ absent

Y – yes/ present

CASES

SL NO	HOSPITAL NUMBER	AGE IN YEARS	PARITY	POG IN WEEKS	FUNDAL HEIGHT	USG POG IN WEEKS	USG EFW IN KG	AFI IN CM	DOPPLER CHANGES			MODE OF DELIVERY	BIRTH WEIGHT IN KG	PLACENTA WEIGHT IN GRAMS	GROSS PLACENTA CHANGES			MICROSCOPIC CHANGES									
									Umb A	MCA	CPR<1				HEM	INF	CAL	HYA	IVF	PVF	SYN	BM	FIB NEC	CAL	INF	HEM	VIL DEG
1	99314	35	G2P1L1	39+6	TERM	37	2.7	11	n	n	N	CS	2.34	400	N	N	N	Y	N	N	N	N	N	N	N	N	N
2	99962	25	PRIMI	39+5	TERM	36	2.3	15	n	n	N	CS	1.94	350	N	N	N	N	Y	N	Y	Y	N	N	N	N	N
3	105781	22	PRIMI	38+2	36 WKS	35	2.7	10	n	n	N	VD	2.44	400	N	Y	Y	N	N	N	N	N	Y	Y	Y	N	N
4	114606	20	PRIMI	38+2	32 WKS	35	2.3	7	n	n	N	VD	2.35	420	Y	N	N	N	N	N	N	N	N	N	N	Y	N
5	115113	19	PRIMI	39	34 WKS	32	1.8	12	n	n	N	VD	2.00	380	N	N	N	N	N	Y	N	N	N	N	N	Y	N
6	115205	23	G2P1L1	39+4	TERM	35	2.25	11	n	n	N	CS	2.30	400	N	N	N	N	N	Y	N	N	N	N	N	N	N
7	115672	30	PRIMI	39+1	32 WKS	34	2.3	3	↑PI	n	N	CS	1.98	350	Y	N	N	N	N	Y	N	N	N	N	N	Y	N
8	110966	20	PRIMI	37+4	30 WKS	32	1.8	6	↑SD	n	Y	CS	1.30	260	N	N	Y	Y	N	Y	Y	N	N	N	N	N	N
9	116201	23	PRIMI	37+1	34 WKS	34	2.2	6	↑PI	↓PI	N	CS	2.00	350	Y	N	N	N	N	N	Y	N	Y	Y	N	Y	N
10	116365	20	PRIMI	37+5	34 WKS	32	2.8	13	n	n	N	VD	2.20	300	N	N	N	Y	N	N	N	N	N	Y	N	N	N
11	120497	29	G3P2L2	38+3	32 WKS	32	2.2	10	n	n	N	CS	1.80	280	N	N	N	N	N	Y	Y	N	Y	N	N	N	Y
12	120477	20	G2A1	40+3	32 WKS	33	2	8	n	n	N	VD	1.99	300	N	N	N	N	N	N	N	N	N	N	N	N	N
13	122669	24	G2P1L1	40+1	34 WKS	36	2	3	n	n	N	CS	2.40	320	N	N	N	N	N	N	N	N	N	N	N	N	N
14	123077	23	G2P1L1	38+4	36 WKS	35	2.2	11	n	n	N	CS	1.96	280	N	N	Y	N	N	N	Y	N	N	Y	N	N	Y
15	134173	22	G2P1L1	37+1	30 WKS	32	2	2	↑PI	n	N	CS	1.95	280	N	N	N	N	N	Y	Y	N	Y	N	N	N	Y
16	1021228	20	G2A1	37+6	36 WKS	36	2.4	2	n	↓PI	N	CS	2.40	400	N	N	N	N	N	Y	N	Y	N	N	N	N	N
17	134402	23	PRIMI	40	TERM	38	2.4	8	n	↓PI	N	CS	2.20	400	Y	N	N	Y	N	Y	N	N	N	N	Y	Y	N
18	149088	20	PRIMI	40+3	36 WKS	35	2.5	6	n	N	N	VD	2.03	250	N	N	Y	Y	N	Y	N	N	N	Y	Y	N	N
19	149060	22	G2P1L1	38+5	32 WKS	37	2.4	10	n	↓PI	N	VD	2.30	350	N	N	Y	Y	N	Y	N	N	Y	Y	N	N	N
20	153766	30	G2P1L1	39	32 WKS	34	2.3	11	n	n	N	CS	1.96	280	N	N	Y	Y	N	Y	N	N	Y	Y	N	N	N
21	161757	25	PRIMI	42	TERM	37	2.4	10	n	n	N	CS	2.19	300	N	N	N	N	N	N	N	N	Y	Y	N	N	N
22	160720	27	G2P1L1	38+5	34 WKS	34	2.4	11	n	n	N	CS	1.90	350	N	N	N	N	N	Y	N	N	Y	N	N	N	N
23	166155	23	PRIMI	38+3	34 WKS	35	2.5	14	n	n	N	VD	2.25	400	N	N	N	N	N	N	Y	N	Y	N	N	N	N
24	170726	20	PRIMI	37+4	30 WKS	33	2.2	10	n	n	N	VD	1.68	250	N	N	N	N	Y	N	Y	N	Y	Y	N	N	N
25	173283	35	G4A3	39+2	30 WKS	32	1.7	2	↑PI	n	N	CS	1.60	200	Y	N	N	N	N	N	Y	N	N	N	N	Y	N
26	182589	28	G2P1L1	40	30 WKS	37	1.8	2	↑SD	n	N	CS	1.73	220	N	N	N	N	N	N	N	N	N	N	N	N	N
27	178247	21	PRIMI	37+3	32 WKS	32	1.9	13	↑PI	↓RI	N	CS	1.80	200	N	N	Y	N	Y	N	Y	N	Y	Y	N	N	N
28	155091	25	G2P1L1	39+1	34 WKS	33	2.2	7	↑PI	n	N	CS	2.00	280	N	N	N	N	Y	N	Y	N	Y	Y	N	N	N
29	183105	26	G2P1L1	37+4	36 WKS	36	2.4	11	n	n	N	CS	1.88	250	N	N	N	N	N	Y	N	N	N	Y	N	N	N
30	186518	25	G2P1L1	37+2	TERM	37	2.5	3	n	n	N	CS	2.37	300	N	N	N	N	N	Y	Y	Y	Y	N	N	N	N
31	189712	20	G2P1L1	41+2	32 WKS	37	2.7	10	n	n	N	VD	2.30	400	N	N	N	Y	N	Y	N	N	N	Y	N	N	N
32	199154	24	G3P1L1A1	37+1	32 WKS	32	2	8	↑PI	n	Y	CS	1.68	280	Y	N	Y	Y	N	N	Y	N	N	N	N	Y	N
33	194270	20	PRIMI	37	32 WKS	35	2.5	10	n	n	N	VD	1.96	280	Y	N	N	N	N	N	N	N	N	N	N	Y	N
34	182051	22	G2P1D1	37+4	32 WKS	32	1.4	5	n	↓PI	N	CS	1.89	400	Y	N	N	Y	N	N	N	N	N	N	N	Y	N
35	203048	22	PRIMI	39+3	TERM	37	2.9	5	n	n	Y	VD	2.30	350	N	N	N	Y	N	N	Y	N	Y	Y	N	Y	N
36	218988	30	G3P2L2	38+2	32 WKS	32	1.86	3	n	n	Y	CS	1.84	280	Y	N	N	N	N	N	N	N	N	N	N	Y	N
37	223463	23	G2P1L1	40+3	34 WKS	36	2.4	4	↑PI	n	Y	CS	1.83	280	Y	Y	Y	N	N	N	N	N	Y	N	Y	Y	N
38	228804	19	PRIMI	38+5	34 WKS	36	2.6	2	n	n	Y	CS	1.90	230	N	N	N	Y	N	N	N	N	N	N	N	N	N
39	238965	22	G2P1L1	38+1	36 WKS	34	2.28	7	↑PI	n	N	CS	1.82	300	N	N	Y	N	N	N	N	N	N	N	N	N	N
40	248740	30	G2P1L1	39+4	32 WKS	36	3	10	n	n	Y	CS	2.40	350	N	N	N	N	N	N	N	N	N	N	N	N	N

CONTROLS

SL NO	HOSPITAL NUMBER	AGE IN YEARS	PARITY	POG IN WEEKS	FUNDAL HEIGHT	USG POG IN WEEKS	USG EFW IN KG	AFI IN CM	DOPPLER CHANGES			MODE OF DELIVERY	BIRTH WEIGHT IN KG	PLACENTA WEIGHT IN GRAMS	GROSS PLACENTA CHANGES			MICROSCOPIC CHANGES									
									Umb A	MCA	CPR<1				HEM	INF	CAL	HYA	IVF	PVF	SYN	BM	FIB NEC	CAL	INF	HEM	VIL DEG
1	78545	19	G2P1L1	40+1	TERM	37	3.4	11	n	n	N	CS	2.90	500	N	N	N	N	N	N	N	N	N	N	N	N	N
2	166168	22	G2P1L1	38+6	TERM	37	3.5	14	n	n	N	CS	2.85	600	N	N	N	N	N	N	N	N	N	N	N	N	N
3	169595	21	G2P1L1	39+6	TERM	38	3.2	8	n	n	N	VD	3.30	480	N	N	N	N	N	N	N	N	N	N	N	N	N
4	82747	24	G2A1	39	TERM	38	3	12	n	n	N	VD	2.91	500	N	N	N	N	N	N	N	N	N	N	N	N	N
5	156411	25	PRIMI	39+4	TERM	38	3.5	9	n	n	N	VD	2.92	500	N	N	N	N	N	N	N	N	N	N	N	N	N
6	190200	26	PRIMI	37+4	TERM	37	2.9	7	n	n	N	VD	2.60	450	N	N	N	Y	N	N	N	N	N	N	N	N	N
7	198718	21	PRIMI	39+4	TERM	39	3	8	n	n	N	VD	2.74	680	Y	N	Y	Y	N	N	N	N	N	Y	N	Y	N
8	198711	22	PRIMI	40+3	TERM	38	3.2	16	n	n	N	VD	3.09	550	Y	N	N	Y	N	N	N	N	N	N	N	Y	N
9	129240	23	G2P1L1	40	TERM	39	3.7	12	n	n	N	VD	3.12	500	N	N	N	Y	N	N	N	N	N	Y	N	N	N
10	206076	28	G2P1L1	40+5	TERM	36	2.7	14	n	n	N	VD	2.68	400	N	N	N	N	N	N	Y	N	Y	Y	N	N	N
11	211582	20	PRIMI	39+3	TERM	37	2.6	10	n	n	N	VD	2.70	450	N	N	Y	N	N	Y	Y	N	N	Y	N	N	N
12	197391	20	G2P1L1	38+4	TERM	36	2.1	11	n	n	N	VD	2.40	400	N	N	N	N	N	N	N	N	Y	N	N	Y	N
13	212245	25	PRIMI	40	TERM	40	3.4	11	n	n	N	VD	2.60	420	N	N	N	N	N	N	N	N	Y	N	N	N	N
14	222810	28	PRIMI	39	TERM	36	2.3	15	n	n	N	VD	2.53	400	N	N	N	Y	N	N	Y	N	N	N	N	N	N
15	229136	20	PRIMI	40+1	TERM	39	3.5	9	n	n	N	VD	2.57	380	N	N	N	N	N	N	N	N	N	N	N	N	N
16	238076	25	PRIMI	38+6	TERM	37	2.5	9	n	n	N	VD	2.40	360	Y	N	N	Y	N	N	N	N	N	N	N	Y	N
17	238124	31	G3P1L1A1	40+3	TERM	38	3	10	n	n	N	VD	3.18	550	N	N	N	Y	N	N	Y	N	Y	N	N	N	N
18	238585	19	PRIMI	38+6	TERM	37	3	7	n	n	N	VD	3.24	500	N	N	N	N	N	N	Y	N	N	N	N	N	N
19	238994	24	PRIMI	40+3	TERM	37	2.8	14	n	n	N	VD	2.68	430	N	N	N	N	N	N	Y	N	Y	Y	N	Y	N
20	242888	19	PRIMI	40+1	TERM	37	2.9	8	n	n	N	CS	2.70	450	N	N	N	N	N	N	N	N	N	N	N	N	N
21	229765	31	G3A2	37+6	TERM	36	2.8	18	n	n	N	VD	2.50	400	N	N	N	N	N	N	N	N	N	N	N	N	N
22	212759	25	G3P2L2	40+3	TERM	40	3.2	10	n	n	N	VD	2.90	410	N	N	N	N	N	N	N	N	N	N	N	N	N
23	208546	24	G3P1L1A1	40+1	TERM	38	3.2	10	n	n	N	VD	3.60	400	N	N	N	N	N	N	N	N	N	N	N	N	N
24	15543	20	G2P1D1	37+1	TERM	37	3	12	n	n	N	CS	2.95	620	N	N	N	N	N	N	N	N	N	N	N	N	N
25	250479	28	G3P1L1A1	38	TERM	31	3.2	14	n	n	N	VD	2.98	470	N	N	N	N	N	N	N	N	N	N	N	N	N
26	254707	23	G2P1L1	37+2	TERM	36	2.8	10	n	n	N	CS	2.40	350	N	N	N	N	N	N	N	N	N	N	N	N	N
27	182242	25	G3P2L2	39+1	TERM	39	2.8	9	n	n	N	VD	2.40	350	N	N	N	N	N	N	N	N	N	N	N	N	N
28	255928	25	G2P1L1	37+2	TERM	37	2.8	11	n	n	N	CS	2.90	350	N	N	N	N	N	N	N	N	N	N	N	N	N
29	254618	28	G2P1L1	38+4	TERM	37	3.2	10	n	n	N	CS	3.10	450	N	N	N	N	N	N	N	N	N	N	N	N	N
30	257731	28	G2A1	38+4	TERM	38	2.8	12	n	n	N	VD	2.62	400	N	N	N	N	N	N	N	N	N	N	N	N	N
31	248765	23	G2A1	41+1	TERM	38	3.5	13	n	n	N	VD	3.18	500	N	N	N	N	N	N	N	N	N	N	N	N	N
32	273147	20	PRIMI	39	TERM	38	3.2	10	n	n	N	VD	3.24	500	Y	N	Y	N	N	N	N	N	N	Y	N	Y	N
33	273231	18	PRIMI	39+3	TERM	39	3	12	n	n	N	VD	3.28	600	N	N	N	N	N	N	N	N	N	N	N	N	N
34	266419	25	G2P1L1	39	TERM	38	2.5	8	n	n	N	VD	2.56	450	N	N	N	N	N	N	N	N	N	N	N	N	N
35	208858	20	PRIMI	37+1	TERM	36	3	10	n	n	N	VD	2.46	550	N	N	N	N	N	N	N	N	N	N	N	N	N
36	274178	21	PRIMI	40+3	TERM	38	2.7	12	n	n	N	VD	2.64	500	N	N	N	N	N	N	N	N	Y	Y	N	N	N
37	230527	35	G4P3L3	40+1	TERM	37	3	11	n	n	N	VD	3.30	450	N	N	N	N	N	N	N	N	Y	Y	N	N	N
38	276946	20	PRIMI	41	TERM	37	2.7	16	n	n	N	VD	2.53	450	N	N	N	Y	N	N	N	N	Y	N	N	N	N
39	276091	25	PRIMI	39+1	TERM	38	3.4	8	n	n	N	VD	3.32	600	N	N	N	N	N	N	N	N	Y	Y	N	N	N
40	27772	21	G2P1D1	39+5	TERM	37	3	14	n	n	N	VD	3.01	500	Y	N	N	Y	N	N	N	N	Y	N	N	Y	N