

# Study of Placenta in Intrauterine Growth Restricted Pregnancy

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## ABSTRACT

**Background:** Pregnancy with intrauterine growth restricted fetus is at greater risk for poor Perinatal and long-term outcome than babies with normal weight. Therefore, intrauterine growth restriction is a major global health concern especially in poor and developing Countries. The placental examination can be a great help in identifying growth restricted fetuses.

**Research problem or aim:** The objective of this study is to examine various morphometric and histopathological changes including inflammation in placenta of growth restricted fetuses along with screening for infections, and to correlate these findings with the etiology and fetal outcome in intrauterine growth restriction.

**Method:** In the current study, 53 placenta of normal fetus were compared with 53 placenta of fetus with intrauterine growth restriction. The criteria for intrauterine growth restriction were gestational age more than 32 weeks and all fetuses with weight Less than 10<sup>th</sup> percentile for that gestation. Histopathological examination along with laboratory screening for infections and inflammation was carried out on placenta. Similarly, fetal outcome were determined in normal versus intrauterine growth restricted pregnancy.

**Results:** The placental examination showed calcification in intrauterine growth restricted Pregnancy as well as in normal pregnancy. However, calcification in placenta associated with intrauterine growth restriction was much denser as compare to placenta from normal pregnancy. The absence of intrauterine infection and inflammation along with good antenatal and postnatal care can deliver favourable outcome in pregnancies with intrauterine growth restriction.

**Conclusion:** This research study reaffirms that best prenatal and antenatal clinical practices can overcome social, epidemiological, and pathological determinants in intrauterine growth restriction to deliver better obstetric results in pregnancy and ensuring good quality of postnatal life for mother and fetus.

**Keywords:** Intra Uterine Growth Restriction (IUGR), Fetal Growth Restriction, High Risk Pregnancy, Placental Calcification, TORCH, and HIV infections.

## INTRODUCTION

Intrauterine growth restriction or fetal growth restriction is defined as a fetus whose birth weight is markedly below the normal weight (less than 10<sup>th</sup> percentile) for that gestational age [1,2]. Intrauterine growth restriction occurs in 5–10% of all pregnancies and is associated with significant morbidity and mortality in the perinatal period causing a major public health problem affecting maternal and child health around world especially in less developed part of the world. [1-5]. Intrauterine growth restriction could arise due to several fetal and maternal factors and one of the important reasons for failure of a fetus to attain its genetically determined growth potential could be a placenta [1-6].

The placenta is a vital organ needed for mammalian development with distinctive characteristics such as the lifetime of placenta is short and its size and function changes continuously during the course of gestation. A normal healthy placenta is necessary for overall growth and well-being of fetus, which eventually will lead to favourable out-come in pregnancy [Figure 1A]. Hence, it is the most accurate record of an infant's pre-natal experience and it provides insight into the pre-natal health of the fetus and mother [2,6-8]. Brief summaries of more recent analysis support the long-standing appreciation of the importance of maternal anthropometry to achieve optimal birth weight [9,10]. Earlier studies have shown that by demonstrating the effects of maternal anthropometry on birth Weight are

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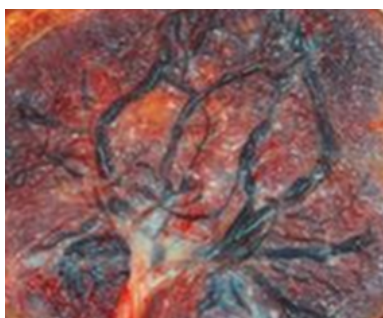
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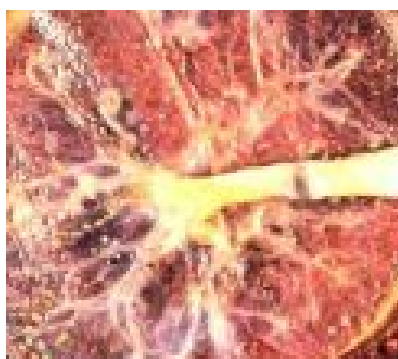
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likely mediated by the effects of both pre-pregnant maternal weight and maternal weight gain on placental volume. These effects operate early in pregnancy and alter both the absolute placental volume at 14 weeks and the rate of placental growth between 17-20 weeks of gestation [7,8,10]. The importance of the outlined etiological factors affecting the placenta has been well understood. Hence, the further study of placental morphology of fetal growth restriction has been selected to determine the value of its association to fetal birth weight. In this study we aim to demonstrate the placental changes in IUGR. Also, it is a well-known fact from previous studies that intrauterine infection and inflammation in placenta along with dense placental calcification [Figure 1B] can have detrimental effects on growing fetus [5,7,8]. Therefore, the objective of this study is to study various histopathological changes including inflammation in placenta of growth [4] restricted fetuses along with screening for toxoplasmosis, other (syphilis, varicella zoster, Parvovirus B19), rubella, cytomegalovirus, Herpes simplex (TORCH) and Human Immunodeficiency Virus (HIV) infections and to correlate these findings with the etiology and fetal outcome in IUGR.



**Figure 1A :** Image Showing Normal Healthy Placenta.



**Figure 1B:** Image Showing Gross Dense Calcification in Placenta.

## MATERIALS AND METHODS

The Director of Academics and Research office at Grant Medical Foundation Ruby Hall Clinic, Pune, India was consulted and approval was taken before conducting this research study in the Department of Obstetrics and Gynecology at Ruby Hall Clinic Pune. In the present study, all the patients that were examined were registered cases

in Ruby Hall Clinic and Urban-Rural Health Centre of Ruby Hall Clinic, Pune, India an appropriate informed consent were taken from the subjects involved in the study. The total number of deliveries reported from February 2007 to February 2008 was 820, and Out of which 53 cases were of intrauterine growth restriction. As a part of routine antenatal check-up and care, all the subject patients in the study were examined for physical signs and symptoms such as fever, excessive weight loss, Hepatosplenomegaly, Lymphadenopathy, Jaundice, and skin rash. Along with their clinical examination, all the patients in the study group were also screened for specific TORCH antigens and HIV infection by doing enzyme-linked immunosorbent assay (ELISA). And these laboratory tests were also part of routine clinical investigation during antenatal check-up and care for all the registered obstetric patients at our hospital. In the current study, 53 placentas of Normal fetuses were compared with 53 placentae of fetuses with intrauterine growth restriction. The criteria for intrauterine growth restriction were gestational age more than 32 weeks and all fetuses with weight less than 10th percentile for that gestation [5]. After carefully selecting the cases, placentae of such patients were studied. About 100 placentae were studied comparing to placental weight with fetal weight. Mothers were screened in the antenatal period and those who were diagnosed having complicating factors such as gestational hypertension, anaemia, and heart disease were admitted in the ward. They were given appropriate treatment after doing relevant investigations and were followed up to delivery. After delivery the neonatologist examined baby. Baby was weighed, sex was noted and the gestational age of fetus was estimated. Placentae of those deliveries were collected for the study. On delivery the placenta was examined immediately in fresh state and the excess blood was washed out under running water. The placenta was weighed and the shape, dimension and color was noted, attachment of cord to the placenta was examined and total cord length was measured, colour of the cord and membranes, presence of true and false knots, and condition of the blood vessels was examined. Next the fetoplacental weight ratio was calculated by using following formula:  $F/P = \text{Weight of fetus in grams} / \text{weight of the placenta in grams}$ . The deciduae and number of cotyledons were examined gross infarcts; haemorrhages, necrotic areas and calcific deposits were looked for. Next the cord and placenta were immersed in 10% formalin for ten days. After the fixation the placenta was examined in to and then cut into sections longitudinally for microscopic evaluation, sections were taken from the centre, periphery, and cord. Additional sections were taken from any abnormal areas and slides were prepared. These slides were stained with haematoxylin and eosin and were mounted under cover slips and finally examined under microscope. On microscopy the following points were noted such [6] as placental infarcts, calcifications, leucocyte infiltration, hyaline change, villus changes, and haemorrhages.

## STATISTICAL ANALYSIS

In the present study the data was analysed statistically using SPSS software version 11 (chi-square test, Z-test) and value  $<0.05$  was considered as statistically significant.

## RESULTS

The results for all the obstetric patients in the study group tested for TORCH and HIV infections were negative. In the current study, the total number of deliveries that took place during the period of study from February 2007 to February 2008 was 820, out of which 53 cases were diagnosed intrauterine growth restriction. This gives an incidence of 6.4% for intrauterine growth restriction in our study. In our study, examination of risk factors showed gestational hypertension 13% in growth restricted fetuses while 5.66% in normal fetuses [Figure 2]. Even though, gestational hypertension is seen more in IUGR pregnancies compared to normal pregnancies, the data is not statistically significant. The placental weight was predicted according to gestational age by ultrasound and compared with actual placental weights in the study group which showed a difference of approximately 70-80 g in predicted placental weight and actual placental weight in grams. It also showed that placental weight is 1/5th of fetal weight [Figure 3]. The Placental thickness was also compared between normal fetuses and IUGR, and it demonstrated that placental thickness is decreased in IUGR [Figure 4], however this data was not statistically significant. In the study group the incidence of central cord insertion is 44.34% in IUGR, while 42.45% in normal fetuses compared to marginal insertion among normal and IUGR (9-7%) that showed high incidence of central cord insertion in [7] study group [Figure 5] with no statistical significance. The histopathological evaluation of placenta in the study group demonstrated that increase in placental calcification in IUGR (22 %) compared to normal placenta (19%) [Figure 6], but statistically this data was not significant ( $>0.05$ ). Although the placenta from both the groups showed calcification, the placenta from fetal growth restricted pregnancy has dense calcification per cotyledon compared to the placenta from the normal pregnancy. Also in this study we failed to quantify the calcification in placenta, because that would have shown the higher density of calcification in IUGR pregnancies compared to normal pregnancies. The fetal outcome in IUGR was also studied which showed that 3.77% of fetuses suffered from Jaundice while 1.89% suffered from Respiratory Distress Syndrome (RDS) and 1.89% had perinatal death approximately 93% fetuses were normal with no anomaly, and TORCH and HIV infections [Figure 7] with no statistical significance. The results presented in this study were not statistically significant, when P value was  $<0.05$ . However, if the P value is  $<0.10$ , then most of the above results showed statistically

significance. This demonstrates that the current study needs more sample size to get statistically significant data to evaluate different variables and their association with IUGR pregnancies and then compare those variables with normal pregnancies. Nevertheless, the current study highlights important parameters regarding placental morphology, along with infection and inflammation associated during pregnancies, and co-morbid conditions that pre-exist in women during pregnancies such as gestational hypertension and heart disease.

## DISCUSSION

A normal placental structure and function is required for the development of a normal healthy fetus at the term. However, if there is an abnormality in placental development, then that could hamper fetal growth and wellbeing resulting in severe complication ranging from IUGR to death of fetus [6,7,11]. IUGR is a common diagnosis seen in obstetrics patients that increases the risk of perinatal mortality and morbidity [2,3]. In most instances, no obvious maternal or fetal cause could be assigned to IUGR, yet gravid mothers present with severe weight loss in fetuses. In such cases, researchers have implicated placenta to be culpable in causing disproportionately low fetal weight resulting in IUGR [2,12]. The placenta is the only vital organ of perinatal life, which can be examined, without hazards to the mother and the baby. However, the placenta provides a paradox as it is one of the most readily available structures for examination, but is one of the least known [8,13,14]. In the earlier study, we had compared placental weight in the study group and it showed that placental weight in normal pregnancy was significantly higher than that in IUGR. We have also shown that feto-placental weight ratio is significantly decreased in IUGR as compared to normal pregnancy. Also, both maximum and minimum diameters of placentae were studied which showed that the placental diameters were less in IUGR as compared to normal fetuses. So, our previous study has shown that indeed the placental anthropometric characteristics such as weight, diameter along with feto-placental weight ratio is closely associated with the normal growth and development of the fetus [2]. In the present study, 53 placentae from normal pregnancy were compared with 53 placentae from pregnancies with IUGR. In this study we did measure the placental thickness in the study group, and we determined that placental thickness was less in [9] IUGR compared to normal fetuses. However, this difference was not statistically significant. Also, the small difference in the thickness that we observed between IUGR and normal placentae could become insignificant due to progressive arborisation of the Villous branching to provide adequate nutrient to support normal fetal growth [7].

Placental disc thickness is an indirect measure of the extent of development of the nutrient exchange surface

of the placenta essential to its successful support of fetal growth. Any abnormal change in the thickness either thin or thick placentae have been correlated to adverse pregnancy outcome [7,15]. We also studied the position of umbilical cord insertion in to the placenta. And we

observed that most of IUGR placentae were with umbilical cord inserted centrally as compared to marginal. None of the IUGR placentae showed eccentric or villamentous insertion.

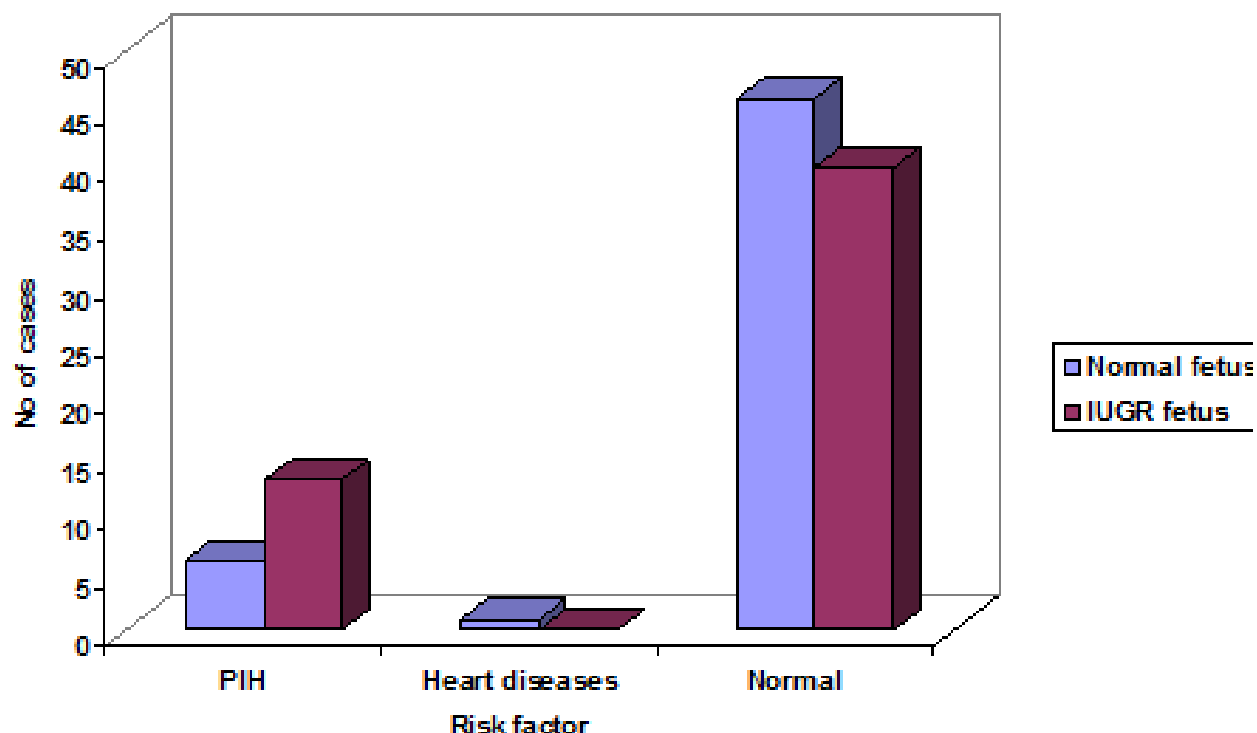


Figure 2: Multiple bar diagram showing Risk factors in study group.

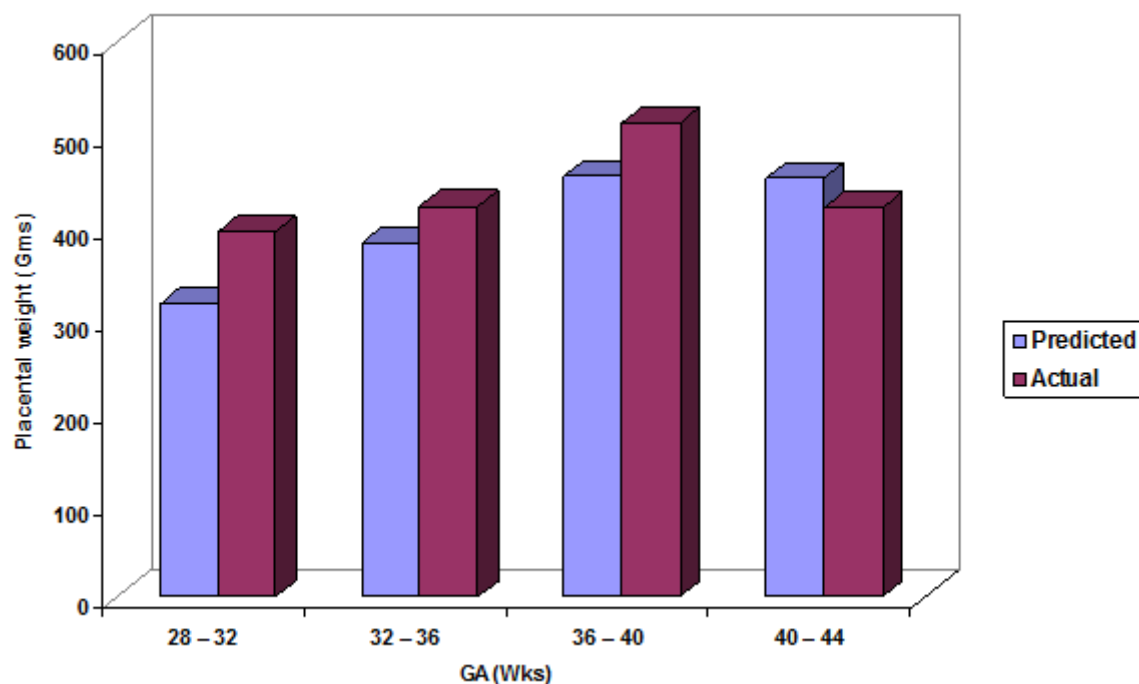
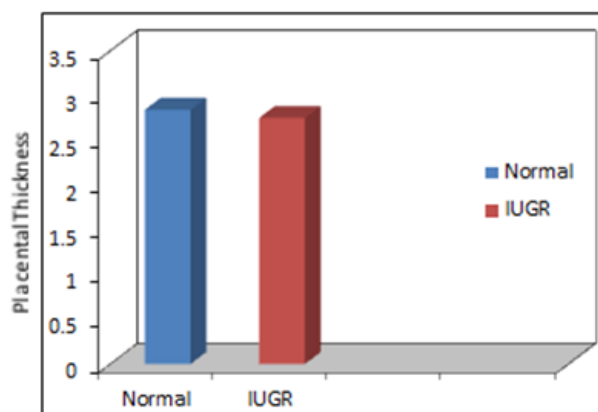
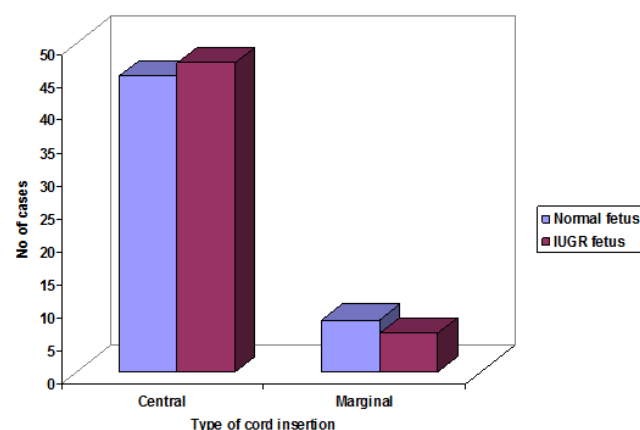


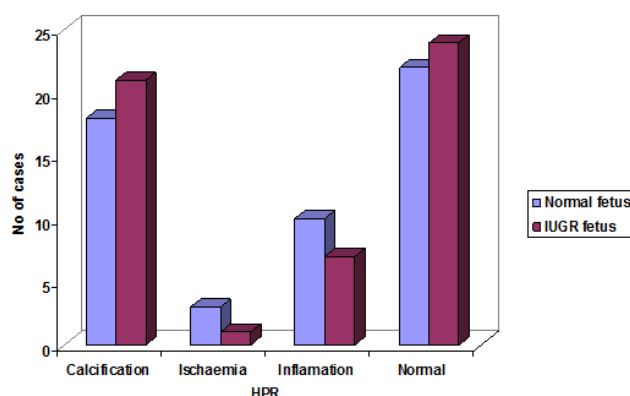
Figure 3: Multiple bar diagram showing GA wise predicted and actual placental weight in study group.



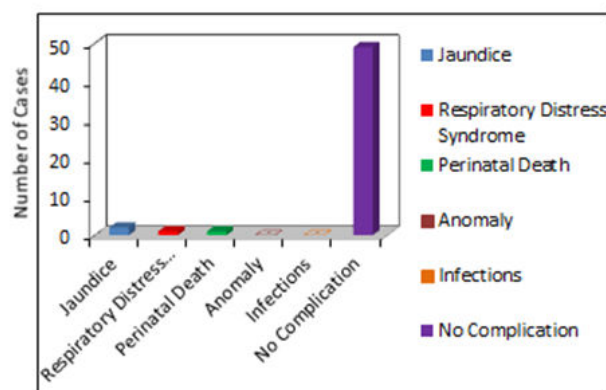
**Figure 4:** Bar diagram showing comparison of placental thickness in the study group



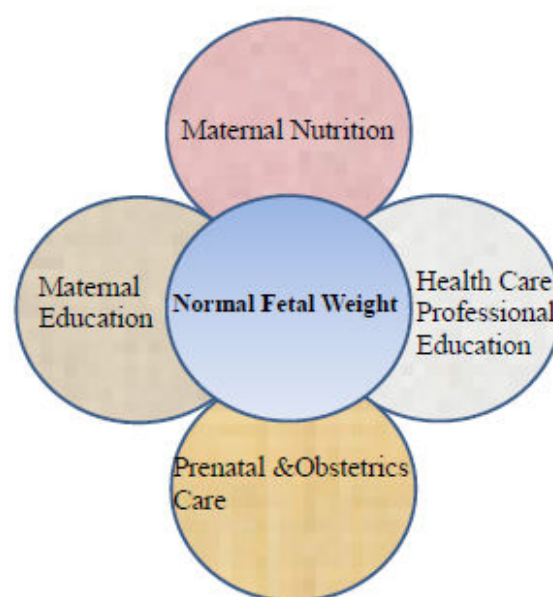
**Figure 5 :** Multiple bar diagram showing type of cord insertion in study groups



**Figure 6 :** Multiple bar diagram showing histopathological evolution of placenta in study group.



**Figure 7:** Bar Diagram showing fetal outcome in IUGR Fetus



**Figure 8:** A schematic diagram illustrating 360 degree Interventional Program with Health Care Professional - Pregnant Woman Partnership to Achieve "normal Fetal Birth Weight"

However studies done by Bjoro, and Davis et al. , showed villamentous and marginal insertion for umbilical cord respectively are more common in IUGR [6,16,17]. In the histopathological examination we came across more cases of placental calcification in IUGR as compare to normal placentae; however, the data was not statistically significant. We also noticed the amount of calcification in placenta per cotyledons was much higher in IUGR as compared to normal pregnancy. But this high incidence of calcification that we observed in IUGR in our study could be due to maternal factor such as gestational hypertension [14,18,19]. Also based on this study results, we recommend to quantify the calcification in placenta as oppose to just grossly visualize the presence of calcification, because quantifying the density of calcification per cotyledon of the placenta would correctly determine the extent of calcification in placenta from IUGR pregnancies compare to normal pregnancies.



Some studies have shown <sup>[10]</sup> placental infarction and ischemia in IUGR; however, in our study we could not see any fresh infarction or signs of ischemia in the IUGR placentae. Along with these factors, we have also done studies looking for inflammation and infection in the placenta. We were not able to demonstrate any significant inflammation or characteristics of inflammatory process such as leucocyte invasion profoundly visible in the IUGR placentae <sup>[11,14,20]</sup>. Earlier studies have shown fibrin deposits, infarcts, and over growth of trophoblastic tissue in IUGR placentae. The study also showed nonspecific inflammation of placental villi with loss of vascular bed at syncytiotrophoblast layer resulting in ischemic damage to the placenta <sup>[12]</sup>. Placental ischemia and infarcts were often seen in women with hypertension and with the increase in the severity of toxemia in pregnancy, all the placental changes are exaggerated. However, similar form of placental changes can be even found in normotensive women <sup>[18,19]</sup>. Moreover, it has also been demonstrated that pregnancy with IUGR that is further complicated by maternal gestational hypertension, shows tremendous augmentation in placental aging with exponential decrease in its functional capacity, leading to an abnormal changes and placental inflammation <sup>[14,19]</sup>. Moreover, we also carried out laboratory tests looking for infection commonly affecting placenta and fetal growth, resulting in to IUGR. We tested our patients for TORCH and HIV infection screening. TORCH screening involves testing for various specific antigens for TORCH pathogens. ELISA screening test was carried out for the HIV infection. And since screening tests were negative, no further tests such as PCR, serology, staining, and culture of placenta were done. Along with these laboratory investigations, we also carried out clinical examination of all the subjects patients in the study group for any physical signs and symptoms related to infections. And we did not find any of the above infections <sup>[11]</sup> in the IUGR patients in our study groups. These screenings for TORCH and HIV Infections are necessary because these viral infections can cause serious harm to the growing fetus. TORCH pathogens that stand for Toxoplasma Gondii others like Treponema palladium, Parvovirus B19, Varicella zoster virus, Rubella virus, Cytomegalovirus, and Herpes simplex virus, can even lead to fetal death, organ damage and or serious complications depending on the specific infectious agents. Rubella or German measles in particular can affect multiple organ systems such as cataracts, microphthalmia in eye, cardiac defect, and neurologic defects such as deafness, mental retardation. Intrauterine HIV infection can cause serious complications ranging from spontaneous abortion to still birth. It can also cause IUGR and preterm birth with neurodevelopmental delay in newborns <sup>[21,22]</sup>. Also, many researchers have shown strong correlation between chronic villitis, acute chorioamnionitis, and abnormal vaginal microflora with IUGR. These intrauterine infections can release various pro-inflammatory cytokines

that can initiate an inflammatory response resulting in preterm labor, and injury to the fetal lung and brain along with increased risk of developing Type 1 diabetes in childhood <sup>[7,21,22]</sup>. Furthermore, in this study, we have also examined various maternal factors such as gestational hypertension and heart disease that have been previously implicated in IUGR <sup>[3,5]</sup>. In our study, cases of gestational hypertension were seen in IUGR compare to maternal heart disease; however, due to less sample size, this data was not statistically significance. The accumulating evidence shows that deviations in birth weight are associated with a host of life long risk that have improved our understanding of the determinants of birth weight essential to appraise major public health risks like <sup>[12]</sup> hypertension and cardiovascular disease affecting communities worldwide <sup>[2,4,5]</sup>. The number of deliveries during the study period was 820 among which 53 were fetal growth restricted pregnancies. Therefore, the incidence in our study was 6.4%, which was comparatively much lower than average incidence of IUGR (10-30%) in our specific geographic region of the world including Southeast Asia <sup>[2,4,5]</sup>. Subsequently, we also compared predicted placental weight with the actual placental weight for that particular gestational age determined by USG. And we found that in our study group, the actual placental weight was always greater than predicted placental weight. Additionally, we also studied the fetal outcome in IUGR. The parameters taken into consideration were jaundice, respiratory Distress Syndrome (RDS), anomaly, infections, and perinatal death. Also we found that only 3.77% fetuses presented with jaundice, 1.89% with RDS, and 1.89% died perinatally. However, majority of the fetuses with 94.3% were absolutely normal with no anomaly, infection, and had no complications. Thus, in our study the low incidence rate along with greater actual weight of placenta than the predicted weight and finally the favourable outcome in pregnancies related to IUGR was due to good obstetric care, NICU facilities and good health care professional staff in the Department of Obstetrics and Gynecology at our hospital that were well trained to manage such high risk pregnancy and obstetric emergency. Moreover, the significance of this article is that the authors of this research study promote a 360° intervention in overcoming this prevalent but preventable public health issue through better health care professional-pregnant woman partnership during pregnancy [Figure 8]. These all-rounded interventional strategies are based on good clinical practices and preventive medicine foundation that will demonstrate that <sup>[13]</sup> early intervention in pregnancy during antenatal visits by incorporating early assessment of placental morphology along with histopathological examination for placental infection and inflammation in conjunction with good obstetric and perinatal care can lead to good prognosis in pregnancy with intrauterine growth restriction. Moreover, the article also recommends that the health care professionals such as physicians, physician assistants (PA's), nurses, and

midwives working in the rural and underserved areas with poor medical infrastructure and clinical facilities should be trained properly to diagnose fetal well-being on the basis of placental morphological and histological changes. Furthermore, academically, more emphasis should be given on incorporating advance knowledge about the placental anatomy, pathophysiology and clinical importance in medical curriculum. Therefore, the medical and allied health students from PA, nursing, and midwifery studies programs will be well versed with the importance of placenta in determining fetal well-being. In accordance with above policy, the authors also suggest that more basic science as well as clinical research involving in-depth study of placenta in IUGR pregnancies should be carried out and presented. It would then serve as an excellent educational tool for medical and allied health care students and budding clinicians by imparting valuable knowledge about intrauterine fetal growth restriction along with importance of placenta and its clinical implications in deciding outcome of the pregnancy. The other important components of this 360 degree interventional program are maternal education and nutrition. This can be achieved through stronger partnership between health care professionals and patient population (pregnant women) by bringing these two groups together through initiating health literacy, wellness education, and increasing competency in clinical practice. As a part of health literacy <sup>[14]</sup> program, health care professionals such as physician, PA, nurses, and public health professionals should initiate dialogue and offer health counselling for women of childbearing age stating different aspects of normal pregnancy and its complications such as IUGR. Also, educating mothers and their family members regarding maternal nutrition and its effects on placental morphology, which in turn will affect the growth and development of their fetuses, should be part of the mother-baby wellness program during their antenatal visits.

## CONCLUSION

In summary, the structural and functional characteristics of the placenta provide insight into the prenatal health of fetus and mother. Also, we know from earlier studies that IUGR is serious obstetric complication and a global health problem especially in less developed region of the world such as Africa, Latin America, and Southeast-Asia. Also the public health issues during antenatal periods such as social factors like maternal poverty, education, and biological factors such as maternal nutrition, infection, inflammation, and other predisposing conditions like gestational hypertension can play a major role in increasing the prevalence and incidence of IUGR in and around this geographical distribution <sup>[2-5]</sup>. Therefore, the significance of this research study is that it reaffirms that best clinical practices that includes prompt diagnosis and management can overcome epidemiological, socio-

behavioural and other pathological determinants in IUGR and deliver better obstetric results encompassing both maternal and child health. The current study of placental morphology at gross and microscopic level along with its functional status in IUGR is an important indicator of intra-uterine growth environment irrespective of antenatal high risk factors. Placental assessment provides a useful <sup>[15]</sup> parameter against which the relative value of various antenatal tests for insufficiency can be reviewed. Unfortunately, none of these tests in itself is completely reliable. But, by helping to delineate the problem of IUGR and by assessing extent of placental growth failure, pathological change in the placenta or a combination of both, a more basic approach to the problem can be achieved. In addition, it should be possible to examine the above placental changes in mothers with known clinical condition and eventually, observe these women in subsequent pregnancies to determine which type of insufficiency is likely to recur. Apart from placental size, changes in placental function would also modify fetal growth. However, in future more studies needed to be done on various qualitative and quantitative aspects looking for structural, functional and metabolic changes in placenta in IUGR and incorporating socio-behavioural and socio-cultural elements affecting maternal health in the study. Thus, we conclude that the basic study of placental morphology and histopathological examination looking for placental infection and inflammation in IUGR carried out by skilled medical professionals' forms an integral part of good prenatal and obstetric care. This clinical intervention during pregnancy along with maternal wellness program including reproductive health literacy would provide a unified action encompassing 360 degree interventional program targeted toward scurtailling IUGR, and promoting favourable fetal outcome in pregnancy.

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## DISCLOSURE

Authors have no conflict of interest to disclose.

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