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Risk Factors for Intrauterine Growth Restriction and Its Neonatal Outcome

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Abstract

Introduction: IUGR is the failure of the fetus to reach its growth potential. Fetal growth is regulated at multiple levels. Besides maternal disorder, fetal structural and chromosomal anomalies are the added factors. The morbidities associated with IUGR could have long term implications in adult life which predisposes in a development of a number of chronic diseases.

Objectives: To identify the various risk factors for IUGR and its neonatal outcome.

Methodology: It is a prospective study conducted in the Department of Obstetrics and Gynaecology, College of Medical Sciences, Chitwan, Nepal in which total of 60 cases of clinically diagnosed IUGR were enrolled during the study period of 2yrs.

Results: The study revealed maximum number of cases (38.3%) belonged to age between 26 to 30 years. IUGR was common in Multigavida (75%), rural area (78.3%), lower socioeconomic status (63.3%) and in manual worker (56.7%). Maternal (41.66%) was the commonest followed by Placental (16.66%) and Fetal (1.66%) causes. IUGR was observed in 43.3% with normal AFI and severe oligohydraminos <5 cm was observed in 21.7%. Doppler velocimetry showed abnormal umbilical S/D ratio in 2 (15.38%). Most of the patients (61.66%) required caesarean section. A total of 36 (60%) neonate had birth weight ranging between 2.5 to 3.0 kg and 83.01% had asymmetrical IUGR. Fifteen (25%) neonates had morbidity but there was no mortality.

Conclusion: Even though IUGR continued to be a challenge and could be tackled with systemic approach and needful management, especially with the help of Ultrasonography and Doppler velocimetry.

Keywords: IUGR (Intrauterine Growth Restriction); SGA (small for gestational age); Neonatal outcome

Introduction

Intrauterine growth restriction (IUGR) is defined as the failure of the fetus to reach its growth potential. IUGR is caused by multiple adverse effects on the Fetus. In the literature IUGR and SGA (Small for Gestational Age) has been used interchangeably, although related they are not synonymous. SGA describes an Infant whose weight is lower than population norms or lower than a predetermined cut off weight. SGA infants are defined as having a birth weight below 10th percentile for Gestational Age or >2 S.D below the mean for Gestational Age [1].

Fetal growth is regulated at multiple levels and successful placentation is mandatory for coordination between key component of Maternal, Fetal, and Placental components. Several conditions may interfere with normal placentation and lead either to pregnancy loss or IUGR. Causes of IUGR are broadly categorized into Maternal, Placental and Fetal causes. Maternal cause could be due to placental vascular insufficiency like Pre-eclampsia, Chronic HTN, Chronic Renal Diseases etc., or it may be due to Malnutrition, Smoking, Alcohol intake etc. Placental cause includes cases of poor uterine blood flow to placental site for a long time leading to chronic placental insufficiency with inadequate substrate (Glucose, Amino acid and Oxygen) transfer as in Placenta previa, Placental infarct, Circumvallate placenta, Chorioangiomata or Velamentous cord insertion [2-4]. Fetal cause is when there is substrate in the maternal blood which crosses the placenta but is not utilized by the fetus like in Chromosomal anomalies (trisomy 13/18/21) or Congenital malformations (cardiovascular disease, renal disease) [4].

Historically, IUGR has been categorized as Symmetrical or Asymmetrical depending upon the onset or etiology of a particular fetal insult. Symmetrical, in which newborn is symmetrically small and have normal Head to Abdomen and Femur to Abdomen ratio. Asymmetrical, in which Head and Long Bones are spared compared with their Abdomen and Viscera [2-4]. In the instance of symmetrical growth restriction, an early insult could result in a relative decrease in cell number and size, with proportionate reduction of both head and body size. Asymmetrical growth restriction might follow a late pregnancy insult with preferential shunting of oxygen and nutrients to the brain, which allows normal brain and head growth so-called brain sparing. The fetal brain is normally relatively large and the liver relatively small. Because of brain-sparing effects, asymmetrical fetuses were thought to be preferentially protected from the full effects of growth restriction. Dashe et al. [5] analyzed 8722 consecutive live born singletons and found that, symmetrically growth-restricted fetuses

were not at increased risk for adverse outcomes compared with those appropriately grown and concluded that asymmetrical fetal-growth restriction represented significantly disordered growth, whereas symmetrical growth restriction more likely represented normal, genetically determined small stature.

IUGR can lead to multiple complications either during Antenatal, Intranatal or Postnatal period. It is associated with increased perinatal mortality and morbidity. During Antenatal period there is risk of Chronic Fetal Distress and even Fetal Death. During Intranatal period there may be Meconium Aspiration Syndrome, Asphyxia, RDS, Hypoglycemia, Hypothermia, Bronchopulmonary Dysplasia, Hyper viscosity-thrombosis. Late complications may include increased risk of Metabolic Syndrome in adult life, Obesity, Hypertension, Diabetes, CHD [2].

The morbidity associated with the IUGR of those that are born alive can cause short, medium and long-term problems, and predisposes to the development of a great proportion of chronic disease in adult life. Therefore, IUGR has important implications not just for the fetus, baby, child and adult, but also for parents, careers and society. Having kept in view the above presentation, the present study was undertaken in order to find out the prevalence of IUGR among high risk mothers and its causal relationship associated with various high risk factors and its Perinatal outcome [6-10].

Objectives of Study

To identify the risk factors for IUGR and its neonatal outcome.

Material and Methods

It's a prospective analytical study conducted at College of Medical Sciences Teaching hospital at Bharatpur, Nepal over a period of 2 years. Patients with Singleton pregnancy from 28th weeks till terms, Longitudinal lie of Fetus and without uterine malformation were included in the study, where as those with Multiple gestations, Hydraminos, Placenta previa, Fetal Malformation, Eclampsia, and PROM were excluded from the study. The ethical clearance for the study was taken from the Institutional Review Board, Committee of College of Medical Science -Teaching Hospital. Informed consent was taken from each patient or their accompanying relatives.

All cases of IUGR pregnancies who attended in Antenatal OPD with high risk factors were interrogated for the study. A detail history was taken as per questionnaire, which included Age, Gravida, Parity, Gestational age, Previous history of IUGR, Last menstrual period, Menstrual history and regularity of the cycle, Significant past medical history, Significant family history and Personal history like Drug abuse, Smoking, Alcohol intake, Socioeconomic status etc. Gestational age determination was based on the best estimate from a reliable menstrual history, and confirmed by a Fetal dating scan done early in the first trimester.

General examination were done which included BP, Weight, Body mass index, clinical evidence of Anemia, Icterus and Pedal edema. Weight of the patients was measured in each antenatal visit. It was estimated to gain 2 kg in each 4 weeks POG. Any stationary weight gain or at time fall during second trimester was suspicious of IUGR. Systemic examination included Cardiovascular and Respiratory systems.

Abdominal examination included Symphysis Fundal height, Abdominal girth, Fetal heart rate, Lie of fetus and its presentation.

Symphysio-fundal height (SFH) was serially measured at each antenatal visit. It was measured in centimeter from top of the uterine fundus to the upper border of the pubic symphysis after its centralization. The numbered side of the tape was placed against the patient's skin to eliminate bias. The symphysio-fundal height was expected to coincide with the period of gestation between 18 and 30 weeks. A clinical lag of fundal height of 4 cm or more was considered suspicious of IUGR.

Abdominal girth was measured at the level of umbilicus beyond 30 weeks. Abdominal girth was expected to increase by 2.5 cm per week beyond 30 weeks and reaches 95-100 cm at term.

Data thus obtained were recorded in predesigned and pretested Performa. The cases who required hospital admission were admitted in maternity ward where routine and special investigation were carried out in the form of CBC, detail Urine RME, Urine culture, VDRL, Glucose challenge test, oral glucose challenge test if required. Blood urea and Serum creatinine, Uric acid, LDH, Liver function test, 24 hours urinary protein, Creatinine clearance test, anaylysis for TORCH infection, Fundoscope examination wherever required.

Ultrasound for fetal biometry was carried out in all pregnant women with IUGR. Ultrasound estimation of fetal parameters like BPD, FL, Abdominal circumference, Amniotic Fluid Index and estimated fetal weight were obtained. These parameters were reassessed at an interval of 4 weeks, or earlier, depending upon the clinical situation to assess the interval growth. BPD was measured at the level of paired thalami and cavum septi pellucidi, from the outer edge of the cranium nearest the transducer to the inner edge of the cranium farthest from the transducer. In Femoral length, the entire length of ossified diaphysis of femur was measured. Abdominal circumference was measured with the transducer in trans-axial scan at the level of liver which included the intra hepatic umbilical portion of the left portal vein and stomach bubble and measurement were taken along the outer edge of the abdomen. Measurement of Amniotic fluid Index was done by summing the largest cord free vertical pocket in each of the four quadrants of an equally divided uterus. AFI of less than 5 cm was taken as abnormal. Fetal Doppler was carried out weeks in women having AFI less than 5 cm.

Doppler Velocimetry of fetal umbilical artery was performed only in patients with AFI less than 5 cm. The umbilical artery measurements were made from free loop of umbilical cord when there was no fetal movement, no fetal breathing excursions and fetal heart rate within normal limits. S/D ratio was computed by dividing maximal systolic flow by minimal end diastolic flow.

S/D Ratio=max systolic velocity/ min diastolic velocity

Umbilical artery S/D ratio above 3 S.D. of the mean were taken as cut off for normal values.

All cases of IUGR were given Bed rest, High protein diet, Arginine supplementation beside Iron, Calcium and Folic acid. Effort was made to continue pregnancy till 37 completed weeks. However in the event, if cases went into Preterm labor, they were managed with Tocolytics, Sedation, Dexamethasone administration to enhance pulmonary maturity. All cases received intensive intra partum monitoring including recording of Partograph and the presence of Pediatrician at the time of delivery. Otherwise, at term the cases were scheduled either for vaginal delivery or caesarean section depending upon their obstetric profile and bishop's score and same were recorded with reasons in the prescribed Performa.

Following delivery, APGAR score was recorded by attending Pediatrician. Neonates were evaluated for Weight, Height, Head circumference and Abdominal circumference.

The Placenta was looked for any Morphological abnormalities, Weight and if required, Placenta was sent for Histopathological examination.

All neonates who required NICU care were strictly followed up till date of their discharge.

Result

In our study we had a total of 87 pregnant women suspected of having IUGR based on clinical examination and/or those having risk factors. We excluded 20 cases because of the presence of exclusion criteria (PROM 10, Placenta previa 4, Multiple gestations 2, Fetal Malformation 2 and Eclampsia 2). Five patients were lost during follow up and 2 patients denied consent and hence totals of 60 patients were analyzed.

Maximum number of cases (38.3%) belonged to Age group between 26 to 30 years followed by age group of 20-25 years. There were only 15(25%) cases of teenage pregnancy. Out of 60 cases, 45 (75%) of the patients were Multigavida and mostly were in the group Gradiva 2 to Gravida 3 (58.3%). Those who lived in the rural area (78.3%) and with lower socioeconomic status (63.3%) had high incidence of IUGR. There were total of 34 (56.7%) cases out of total IUGR cases that belonged to manual worker as opposed to rest 26 (43.4%) from Housewife and Sedentary worker as shown in Table 1. In the present study, however maximum cases 36 (60%) belonged to normal BMI as opposed to 22 (36.71%) with lower BMI. Total of 10 (16.7%) patients were chronic smoker who developed IUGR as opposed to 50 (83.3%) who did not show history of smoking and only 7(11.7%) cases of chronic alcoholic had IUGR pregnancies.

Variables	No of Pts (n=60)	Percentage (%)
Age (In years)		
<20	15	25.0
20-25	11	18.3
26-30	23	38.3
31-35	9	15.0
>35	2	3.3
Gravida		
G1	15	25.0
G2-G3	35	58.3
G4-G5	10	16.7
Rural	47	78.3
Socioeconomic status		
Upper	8	13.3
Middle	14	23.3
Lower	38	63.3
Occupation		
Manual worker	34	56.7
Housewife	19	31.7
Sedentary worker	7	11.7
BMI		
<18.5	22	36.7
18.5-25	36	60.0
26-30	1	1.7
>30	1	1.7
Smoking	10	16.7
Alcohol intake	7	11.7
SFH		
Normal SFH	5	8.33
<2 cm	7	11.66
2-4	30	50
>4 cm	18	30
USG AFI		
<5 cm	13	21.7
5-8 cm	12	20.0
9-12 cm	9	15.0
>12 cm	26	43.3
Doppler velocimetry (S/D ratio)		
<1	9	69.23
1-3	2	15.38
>3	2	15.38

Table 1: Demography of the patient with IUGR.

In total of 60 cases of IUGR, discrepancies of Fundal height with respect to current gestational age were observed in 55 (91.66%) cases. Severe discrepancies of more than 4cm were observed in 18 (30%) followed by 30(50%) between 2-4 cm and 5(8.33%) cases of less than 2 cm cases. It can be observed from the Table 1 that even with a normal Amniotic fluid index (>12 cm), IUGR was observed in 26 (43.3%) of cases. However in 34 (56.7%), there were low Amniotic fluid index with IUGR. Severe oligohydraminos <5 cm was observed in 13(21.7%) of cases and only these patients undewent Doppler velocimetry. Doppler velocimetry was done to ascertain for any evidence of any fetal compromise. Only 2 (15.38%) out of 13 cases showed abnormal umbilical S/D ratio. In other cases (n=11, 84.62%), though there were USG evidence of severe oligohydraminos, but there were no compromise of Umbilical artery S/D ratio.

Analysis of various principle risk factors among 60 cases of IUGR pregnancies showed no risk factors in 24 (40%) cases; while in 36 (60%) the risk factors belonged to Maternal 25 (41.66%), Placental 10(16.66%) or Fetal 1 (1.66%).

Most significant Maternal risk factor observed was Hypertension complicating pregnancy in 7 (28%) in which 3 (42.85%) were because of severe preeclampsia and 2 (28.57%) were because of chronic HTN and Gestational HTN one each. Maternal HTN was followed by UTI in 6 (24%), Previous history of IUGR and severe anemia (HB <7 gm/dl) in 3 (12%) cases each and then by RHD, Uterine anomaly, obstetric cholestasis, APLA in 1 (4%) each. There was 1 (4%) case of pregnancy with IUGR where mother receive chemotherapy during present pregnancy as shown in Table 2.

Risk factors	No. of pts (n=60)	Percentage (%)
Idiopathic	24	40
Maternal	25	41.66
Maternal HTN	7	28
Previous history of IUGR	3	12
Severe anemia	3	12
Chronic renal disease	1	4
UTI	6	24
RHD	1	4
Uterine anomaly	1	4
Obstetrics cholestasis	1	4
APLA	1	4
Drug intake (chemotherapy)	1	4
Placental	10	16.66
Placental infarct	7	70
Circumvallate placenta	2	20
True knot	1	10
Fetal (TORCH infection)	1	1.66

Table 2: Analysis of Risk factors.

Out of 10 (16%) cases of placental factors associated with IUGR, Placental infarct in 7 (70%) was the major cause as opposed to Circumvallate placenta in 2 (20%), and True knot of umbilical cord in 1 (10%). These observation was made after the delivery of placenta.

Most of the cases, i.e. 42 (70%) delivered at term between 38 to 40 weeks period of gestation as opposed to 15 (25%) cases between 35 to 37 weeks. There were only 3(5%) cases who delivered at 41 to 42 weeks period of gestation. As can be seen from the Table 2 only 8(13.33%) cases went into spontaneous labor as opposed to 28 (46.66%) cases that required Induction of labor. Total of 23 (38.32%) cases underwent vaginal delivery of which 7 (11.66%) cases had instrumental delivery. There were total 37 (61.66%) cases of caesarean section of which 13 (21.66%) were Emergency caesarean section performed during their labor. There were total 24 (40%) cases that went for elective caesarean section for various indications. Various indication for elective caesarean section in the present study were severe oligohydraminos in 13(54.16%) cases which was the most common indication followed by poor bishop score in 4(16.66%) cases, post caesarean section in 3(12.5%) cases , BOH in 2(8.33%), Uterine malformation and chronic renal disease in 1(4.16%) each (Table 3).

Variable	No. of pts (n=60)	Percentage (%)
POG(weeks) at delivery		
35-37	15	25
38-40	42	70
41-42	3	5
Mode of termination		
Spontaneous labour	8	13.33
Induction of labour	28	46.66
Elective Caesarean section	24	40
Mode of delivery		
Normal delivery	16	26.66
Forcep delivery	1	1.66
Vacuum delivery	6	10
Elective caesarean	24	40
Emergency caesarean	13	21.66
Indications for Elective caesarean		
Severe oligohydraminos	13	54.16
Poor Bishop score	4	16.66
Post caesarean section	3	12.5
BOH	2	8.33
Uterine malformation	1	4.16
Chronic renal disease	1	4.16

Table 3: Termination of pregnancy.

On analysis of neonatal apgar score at 5 min after birth, there were total of 9 (15%) cases with Apgar score between 4-7. Most of these neonates required resuscitation with minimum supportive measures from the attending Pediatrician. In 51 (85%) cases Apgar score was >7 at 5 min after birth. A total of 36 (60%) neonates had birth weight ranging between 2.5 to 3.0 kg as opposed to only 17 (28.33%) of neonate who had <2.5 kg. In contrast to this there were 7 (11.66%) cases, who had their birth weight >3.0 kg.

Asymmetrical IUGR in the present study verified after birth of the newborn. Out of total 60 cases of IUGR pregnant women enrolled for the study, 7 (11.66%) cases did not show any post-natal evidence of IUGR with treatment received at the time of birth. Rest 53 (88.33%) at birth exhibited evidence of IUGR at various degrees even with treatment received earlier. Out of these 53 cases, 9 (16.98%) were Symmetrical IUGR in contrast to 44 (83.01%) had Asymmetrical IUGR.

Out of total 60 cases of IUGR 4 neonate had Birth asphyxia, for which they were admitted to NICU. In addition, 2 developed MAS, 3

had neonatal jaundice, and 6 had neonatal sepsis, for which they were admitted to NICU for their respective management but there were no mortality.

Discussion

IUGR can be defined as birth of an infant at weight which is less than its genetic potential. It encompasses a heterogeneous group of conditions which result in failure of fetus to achieve its genetic potential for growth prenatally. This condition includes inadequate placental function and fetal abnormalities. The prevention of low birth weight was public health priority in many developing countries where the condition was largely attributable to IUGR as compared to prematurity. Consequently it became a challenge to obstetrician to optimize the outcome of these high risk infants by identifying its causes and severity and when inadequate growth occurred. In our study we had 60 IUGR patients per 187 with high risk factors for IURG. IUGR, they observed it in 23.8% of the newborn and that approximately thirty million babies worldwide suffer from IUGR every year. Whereas, Fikree et al. [10] found the incidence of term intrauterine growth retardation was 24.4% among the 738 singleton births.

Relation of Maternal age with IUGR

Fikree and Berendes [10,11] observed significant correlation between maternal ages below 20 years with development of IUGR. In their study they found a total of 1000 pregnant women, an incidence of IUGR of 15.7% below 20 years as opposed to AGA of 10.5% (OR 1.9) whereas Dashe et al. [5] opined that mean maternal age at delivery under 15 and above 35 years did not differ between the AGA and SGA groups. Meis et al. [12] and Odiba et al. [13] observed a definitive risk of IUGR in women of 35 years and above only. The present study observed an incidence of IUGR in women below 20 years in 15 (25%) of cases as opposed to 23 (38.3%) in maternal age between 26-30 years. There were only 2 (3.3%) cases of IUGR in women more than 35 years.

Relation of IUGR with parity

Primipara and Grand Para both had higher OR on the development of IUGR but suggested that age is not an independent determinant of IUGR in study by Fikree et al. [10], where Primipara women had 23.3% incidence of IUGR as opposed to only 12.9% in control women (OR 2.3). However, most of the IUGR cases were in the range of Para 1 to Para 3 in 41.7% of cases. It is widely accepted that Nulliparous women have an increased risk of IUGR by population centiles with OR 1.3 to 2.1 compared with Multiparous women [3]. As opposed to above present study observed that maximum cases i.e. 45 (75.0%) were between Gravida 2 and 3 in contrast to only 15 (25%) in Primigravida.

Relation between geographical distribution and IUGR

The cases collected for the present study were mainly from the hilly terrain of Nepal. It is a general observation that most of the population in Rural Nepal belongs to Hilly terrain and they represent mass population with lower socioeconomic status. They earn their livelihood after intensive manual labor like farming, weight lifting, low literacy, social taboos etc. Therefore it was not unlikely to observe higher incidence of fetal growth deprivation in this group of women. In the present study, out of total 60 cases, 47 (78.3%) belonged to Rural and Hilly terrain as opposed to only 13 (21.7%) belonged to plain area of Nepal.

Relation with socioeconomic status

Low socioeconomic status has been associated with an increase in IUGR [10]. Socioeconomic criteria like quality of housing, paternal employment status, education level, religion, sources of water supply were significantly associated with increased risk. We had 38 (63.3%) cases belonged to lower socioeconomic status [14].

Nature of occupation and IUGR

Literatures suggests that number of biological and behavioral variations like maternal occupation only marginally or not at all associated with risk of IUGR [10,11]. On one hand it has suggested that increased stress associated with busy job could lead to IUGR; on other hand being an unemployed could indicate lower socioeconomic status with perhaps higher risk lifestyles. In the present study, it was observed that the cases engaged in manual labor like agriculture, lifting heavy weights, constructive activities were vulnerable for the development of IUGR. Out of total 60 cases, 34(56.7%) were manual laborer as opposed to 19(31.7%) who were housewife. There were only 7 cases of IUGR that belonged to sedentary worker.

Relation of BMI and IUGR

Low pre pregnancy maternal weight has been implicated implicated cause for IUGR. Fikree and Berendes [10] observed a significant correlation between low maternal weight less than 50kgs and IUGR with OR 2.6 and attributable risk of 38.9% as compared to maternal weight equal or more than 50 kgs with OR >1.0, which is also seen in different other studies [11,15]. A prospective study from China revealed an association between prepregnancy BMI and birth weight. Infants born to women who were severely underweight before pregnancy with BMI <18.5 were of increased risk of IUGR as compared to normal maternal BMI [16]. We also had similar finding where IUGR was present in 22 (36.7%) cases, which were underweight with BMI less than 18.5. However there was no definite correlation between overweight and probability of IUGR, but the cases were too low to draw any definite conclusion [17].

Relation between smoking and IUGR

Smoking had always remained a matter of much discussion on the effect of development of growth of fetus. While on one hand use of Tobacco only marginally not at all associated [18] with risk of IUGR, other [19-30], observed Smoking was a most important risk factor for IUGR in general population. Support for causative role came from Liebermen et al. [31-33], who showed the critical time of exposure was 3rd trimester, highlighting the importance of cigarette smoking even in advanced pregnancy. The decrease in birth weight range from 135-458gms in heavy smokers as compared with non-smokers [7,34]. Further Kleijer et al. [11], also observed a strong co relation between smoking and IUGR with OR 3.24 and CI 2.32-4.54. In the present study, out of total 60 cases, only 10 (16.7%) were chronic smoker. However sample size was too small in number to draw any significant correlation between smoking and IUGR.

Relation of alcohol intake and IUGR

Kleijer et al. [11] opined that Alcohol used primarily for the social drinking was not found to a risk factor. In contrast, he stated that low level of alcohol intake provide protection for conventional IUGR but not customized IUGR in Nulliparous women. Haram et al. [18],

reported alcohol consumption during pregnancy leads to fetal damage and fetal alcohol syndrome with craniofacial anomalies and neurological disorders. According to him, alcohol is most teratogenic during organogenesis, which may destroy placental trophoblastic tissue and reduced placental blood flow and increase in thromboxane production. Also that even an exposure to small prenatal amount of alcohol may be harmful though the minimal amount of alcohol which may cause harm is not yet known. We had 7 (11.7%) cases who were regular taker of alcohol of small to moderate amount of alcohol.

Maternal risk factors

Various maternal factors has been attributed for IUGR. Resnik et al. [7] found that maternal vascular disease, with its associated decrease in uteroplacental perfusion, was believed to account for 20-30% of all IUGR infants. In a population based study done by Gilbert et al. [14], found that the incidence of chronic hypertension was 0.69% (29,842) with increased neonatal morbidity along with IUGR. Mazor-Dray et al. [16] included 199,093 deliveries where 4742 (2.3%) had UTI during pregnancy and delivery, found that patients with UTI had significantly higher rates of IUGR, pre-eclampsia, CD and pre-term deliveries (either before 34 weeks or 37 weeks of gestation). Several studies had shown that women who had an IUGR infant in a previous pregnancy had an increased risk of delivering an IUGR infant in the next pregnancy. The rate of recurrence was believed to be nearly 20 percent [11]. Anemia probably caused fetal stress with increased fetal Corticotropin-releasing hormone, increased cortisol production and oxidative damage to erythrocytes, both inhibiting fetal growth. Singla et al. [19] had 54 anemic (Hb < 11.0 g/dl) mothers who had birth weight, head circumference, chest circumference, mid-arm circumference, and crown heel length were significantly low in infants born to women with moderate and severe anemia. On the other hand, low Hb levels due to physiologic hemodilution were favorable for fetal growth. Low Hb. concentrations (9.0-11.9 g/100 ml) were connected to reduce IUGR development in smokers, probably because of hemodilution and reduced blood viscosity favorable to uteroplacental circulation. Little et al. [20] did a prospective cohort study on 222,614 first singleton pregnancies and found that lowest perinatal mortality was associated with a lowest recorded maternal hemoglobin concentration of between 9-11 g/dL. In the present study, most significant Maternal risk factor observed was Hypertension complicating pregnancy in 7 (28%) in which 3 (42.85%) were because of severe preeclampsia and 2 (28.57%) were because of chronic HTN and Gestational HTN one each. Maternal HTN is followed by UTI in 6 (24%), Previous history of IUGR and severe anemia (HB <7 gm/dl) in 3 (12%) cases each and then by RHD (Rheumatic heart disease), Uterine anomaly, obstetric cholestasis, APLA in 1 (4%) each. There was 1 (4%) case of pregnancy with IUGR where mother receive chemotherapy during present pregnancy.

Placental factors

According to Alferivic et al. [35], placental factors like abruption and placenta previa might be associated with IUGR, though other risk factors like HTN and thrombophilias might be associated. Grivell et al. [36] opined placental diseases and dysfunction attributed to IUGR. In a Hungarian population-based study, 230 (3%) had a sub-chorionic hematoma on a routine first-trimester scan. These women had increased IUGR, 6.9% versus 2.9%. In the present study, 10(16.66%) cases was attributed by placental factors out of total 60 cases of IUGR, where 7(70%) were due to placental infarction, 2(20%) were due to circumvallate placenta and 1(10%) was due to true knot of umbilical cord. Since placenta previa was excluded in the present study, there was no correlation between IUGR and placenta previa.

Fetal cause

Lin et al. [8] had 15-50% IUGR due to fetal cause. In their study, there were 7% of IUGR was due to chromosomal abnormalities and fetal infection were seen in up to 10% of all IUGR. Grivell et al. [36], opined that CMV in pregnancy causes fetal damage throughout pregnancy causing IUGR even without maternal illness indicating need for screening CMV infection in pregnancy. In the present study, as fetal congenital malformation and chromosomal malformation were excluded, only 1 (1.66%) was due to fetal TORCH infection.

Serial measurement of SFH

Jimenez et al. [24] described the simple, safe, inexpensive, and reasonably accurate screening method to detect IUGR, measuring serial fundal height measurement in which fetal growth was suspected with measurement more than 2 to 3 cm from the expected height. Between 18 and 30 weeks, the uterine fundal height in centimeters had shown to coincide within 2 weeks of gestational age. In the present study discrepancies of fundal height with respect to current gestational age were observed in 91.66% cases. Severe discrepancies of more than 4 cm were observed in 30% followed by 50% between 2-4 cm and 8.33% cases of less than 2 cm cases.

Amniotic fluid index on USG

The association between pathological fetal-growth restriction and oligohydramnios is mainly because of diminished fetal urine production caused by hypoxia and diminished renal blood flow. However the bio-physical prophile done by Chauhan et al. [25] in 1859 singletsons found oligohydramnios in less than 10 percent of pregnancies suspected of growth restriction. In the present study 56.7% IUGR cases showed correlation with AFI. Severe oligohydraminos (<5 cm) was observed in 21.7% of cases as opposed to amniotic fluid index between 5 to 8cm in 20% and amniotic fluid index 8-12 cm in 15% of cases respectively.

Doppler velocimetry

In high risk pregnancies, umbilical artery velocimetry with increase S/D ratio ratio >3 identifies IUGR with sensitivity and specificity 78-85% respectively [26]. Absent or reversed end diastolic flow in umbilical artery of IUGR after 30- 32 weeks gestation as it was associated with a very high risk of adverse outcome [37]. In the present study, Doppler velocimetry was performed in 13 (21.7%) cases who had severe oligohydraminos (AFI<5), to ascertain for any evidence of fetal compromise, and out of these only 2(15.38%) had abnormal umbilical S/D ratio, who were delivered via caesarean section. In other cases, though there was USG evidence of severe oligohydraminos, but there were no compromise of umbilical artery S/D ratio and managed accordingly.

Period of gestation at delivery

These is still a controversy on the timing of delivery in the preterm IUGR fetus. On one hand there is fear of compromised maternal-fetal exchange of substrate, while on other hand there is risk of prematurity. After 30-32 weeks of gestational the umbilical artery Doppler may be

the most important indicator of fetal jeopardy [37]. The absent end diastolic flow (AED) is a severe sign suggesting of fetal compromise which outweigh the possible benefit of prolonging the gestation. But it must be consider that delayed delivery results in more still birth at the same time immediate delivery result in more neonatal death. In the present study out of total 60 cases, 42 (70.0%) underwent delivery at term between 38-40 weeks as opposed to 15 (25.0%) were delivered prematurely between 35 to 37 weeks. Incidentally 3(5.0%) cases, the gestation were prolonged between 41 to 42 weeks.

Mode of delivery

Most of the growth restricted fetuses with impaired placental function withstand poorly the stress of labor so the chances for operative delivery is much more frequent among IUGR fetuses. Marsal et al. [37] had 35% of 7022 IUGR pregnancies delivered by caesarean section and 3 % by vaginal instrumental instruction. The mode of delivery could be decided based on the favorability of the cervix, and the severity of the IUGR as judged by the Doppler studies of the fetal vessels and response of the fetus to an Oxytocin challenge test. The positive Oxytocin challenge test for the fetal distress in the umbilical artery Doppler is an indication for operative delivery. If the umbilical artery Doppler showed increased pulsality index only with a negative Oxytocin challenge test and a favorable cervix, then vaginal delivery can be tried [9]. Only 8 (13.33%) of our patents underwent spontaneous labor. Labor was induced for various indications in 28 (46.66%) cases as opposed to elective caesarean section in 24 (40.0%) of cases for different indications with highest 13(54.16%) cases being severe oligohydraminos, 4(16.66%) cases of Poor bishop score, 3 (12.5%) cases of post caesarean section, 2(8.33%) of BOH, 1(4.16%) of uterine malformation and chronic renal diseases each.

APGAR score at 5 min

APGAR score reflexes the hypoxemic status of new born during the stress of labor. It is reliable indicator of placental reserve of the fetus especially in IUGR pregnancies. Kleijer et al. [11], on their univariate analysis of continuous variables in IUGR pregnancies both nulliparous and multiparous women did not find significant difference on mean APGAR score at 5 min between IUGR and the control group. They observed a mean APGAR at 5 min of 9 between conventional and customized group as opposed to control of 9.1 and 9.0 respectively in primiparous women. Whereas in multiparous women APGAR at 5 min were 9.1 and 9.2 in IUGR and 9.2 and 9.1 in control group respectively between conventional and customized group. In the present study out of total 60 cases, APGAR at 5 min was more than 7 in 51 (85.0%) cases as opposed to APGAR of 4 to 7 in 9 (15%) cases. There were no cases with APGAR score of less than 4 in 5 min.

Birth weight during delivery of IUGR

IUGR and SGA are defined as the birth weight less than 10th percentile for gestational age. But one problem with this definition is the variation in birth weight depending upon ethnicity and altitude. Further fetal weight percentile throughout pregnancies also varies between countries to country. Jones and Hayslett et al. [15] studied on 82 pregnancies with suspected IUGR in cases with preexisting primary renal diseases and observed the mean birth weight of them as 2239 ± 839 gms. Further the birth weight below 10th percentile in 37% of infants nearly 4 times the expected weight.

In the present study, all the 60 cases were enrolled after clinically confirmed IUGR and were subjected to appropriate management in the hospital. The cases were admitted at different period of gestation. Therefore the birth weight of infant might not reflect the true status of IUGR as most of them received clinical management since admission. Out of total 60 cases of clinically diagnosed, 36(60.0%) of IUGR neonate had birth weight ranging between 2.5 to 3 kgs as opposed to only 17 (28.33%) of neonate who did not show much improvement in birth weight despite management in hospital. There were 7 (11.66%) cases who did not showed birth weight beyond 3kgs unlikely to the study done by Muhammad and Khattak [29] where their mean birth weight was 1.8 ± 0.33 Kgs.

Symmetrical OR asymmetrical growth restriction

Sonography can be used to determine head-to-abdomen circumference ratio (HC/AC) to differentiate growth-restricted fetuses [17]. Those who were symmetrical were proportionately small, and those who were asymmetrical had disproportionately lagging abdominal growth. In the instance of symmetrical growth restriction, an early insult could result in a relative decrease in cell number and size. They had reduced growth measurements from early in pregnancy, a normal ponderal index, brain growth proportional to body size and low risks for Perinatal asphyxia and neonatal hypoglycemia [21]. Whereas, asymmetrical growth restriction had late-onset growth failure, a low ponderal index, brain sparing and increase risks for Perinatal asphyxia and neonatal hypoglycemia [21]. Asymmetrical fetal-growth restriction represented significantly disordered growth, whereas symmetrical growth restriction more likely represented normal, genetically determined small stature [5,17]. Roza et al. [22] challenged the concept of "brain sparing", where he followed 935 toddlers using the Child Behavior Checklist at 18 months of age and found that infants with circulatory redistribution brain sparing had a higher incidence of behavioral problems. In our study, 7 (11.66%) had no evidence of IUGR after delivery and remaining 53 (88.33%) had IUGR. Among which 9(16.98%) were Symmetrical in contrast to 44 (83.01%) who were Asymmetrical IUGR.

Neonatal complication

Perinatal outcome: Perinatal morbidity and mortality in growth restriction are inversely proportional to percentile of birth weight, with progressive increase in these rates when the fetal weight drops below the tenth percentile towards the first, and more dramatically below the fifth percentile. The immediate neonatal period may present several metabolic disorders and the main sequelae in the long run are reduced somatic growth, hyperactivity of the central nervous system, difficult speech, coordination deficit, reduced attention and even cerebral palsy. The worst outcomes are observed in severe IUGR cases, with extreme prematurity and very low weight, who present important deterioration in umbilical flow [23]. Bernstein et al. [27] examined the association between IUGR and adverse neonatal outcomes in a population of 19,759 singleton very-low-birth-weight neonates without major birth defects. IUGR within the range of 501 to 1500 g birth weight was associated with increased risks of neonatal death, necrotizing enterocolitis, and respiratory distress syndrome. McIntire et al. [28] included a total of 122,754 singleton live infants without malformations between 24 and 43 weeks of gestation and found that the mortality and morbidity were increased among infants born at term whose birth weights were at or below the 3rd percentile for their gestational age. In the present study out of total 60 cases of IUGR

neonate, only 16 neonates suffer from some forms of neonatal complications. Most of them were either birth asphyxia or neonatal sepsis. Five (9%) had birth asphyxia with low APGAR score for which they were admitted in NICU for respective management. In addition 6(10%) had developed neonatal sepsis in immediate post-natal period. MAS was observed in only 2(3.33%) of neonates besides early neonatal jaundice in 3(5.0%) neonates for which they received respective management. There wasn't any neonatal mortality (Table 4).

Variable	IUGR neonate (n=60)	Percentage(%)
APGAR at 5 mins		
<4	0	0
4-7	9	15
>7	51	85
Birth weight (kg)		
<2.5	17	28.33
2.5-3	36	60
>3	7	11.66
Asymmetrical	44	83.01
Neonatal complication		
Birth asphyxia	4	6.66
Neonatal jaundice	3	5
MAS	2	3.33
Sepsis	6	10
No complication	45	75

Table 4: Neonatal outcome.

Conclusion

IUGR is still a challenge to Obstetrician and the society at large due its problems related to its prevention, diagnosis, and its management. The issue had been complicated by the fact that long term follow up studies had shown IUGR babies were more likely to become victims of Heart disease, Chronic HTN, and Diabetes in their adult life. The study observed significant association of IUGR in women in younger age and parity. Most of them were from Hilly areas of Nepal with poor socioeconomic background and engaged in heavy manual agricultural works. Among the various risk factors, maternal HTN with pregnancy, UTI and placental causes were the predominant cause for the IUGR in the present study. In nearly 40% of cases no cause could be identified. Greater number of cases required elective induction of labor and elective caesarean section as preferred mode of delivery. In the study, a good number of cases responded well to hospital management with improvement in neonatal birth weight. Even some neonates exceeded the birth weight of more than 3 kg without any neonatal

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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