



## Original Research Article

# Intrauterine growth restriction: Biochemical, histopathological and ultrasonographic evaluation

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## Abstract

**Background:** Intrauterine growth restriction (IUGR), a condition that occurs due to various reasons, is an important cause of fetal and neonatal morbidity and mortality. This study was done to know biochemical, histopathological and radiological changes in IUGR cases with pregnancy.

**Methodology & Subjects:** Women who attended the Obstetric OPD in their 1<sup>st</sup> trimester of pregnancy and those who were thought would be able to visit the antenatal clinic for their fortnightly check-up regularly were screened for intrauterine foetal growth retardation. Women with irregular and uncertain menstrual history and where the 1<sup>st</sup> trimester USG foetal crown rump length did not corroborate with the menstrual gestational age were excluded from this study.

**Results:** Incidence of IUGR was 18.2% and 84% were found to be asymmetrical. IUGR was found to be double among primigravids and women above 30 years. In the present study, both clinical and ultrasonographic detection of oligohydramnios was found to be associated with IUGR. Abdominal circumference was found to be less in IUGR group than control cases from 28 weeks onwards in serial USG examination. Mean weight of placenta of IUGR babies were significantly low as compared to control group. Hb level was found lower in IUGR cases than control group. Maternal blood sugar level was relatively low at term in IUGR group. In IUGR group perinatal mortality was 2 (8%), whereas in normal pregnancy there was no perinatal death.

**Conclusion:** Fetuses with impaired intrauterine growth resulting from placental insufficiency are at increased risk of adverse short- and long-term outcome. Most of risk factors associated with IUGR in this study are preventable.

**Keywords:** Intrauterine growth restriction (IUGR); Fetus; Pregnancy; Placenta; USG; Outcomes.

## Introduction

Intrauterine growth retardation (IUGR) is defined as a rate of growth of a fetus that is less than normal for the growth potential of a fetus (for that particular gestational age).<sup>1</sup> It is diagnosed by two direct intrauterine growth assessments (ultra-sonographically) or when the fetal length (height) is less than two standard deviations (or third percentile) below the mean for gestational age.<sup>2</sup> IUGR can virtually be caused by any aberration in the normal biological processes that occur during the course of pregnancy and contribute to the growth of the fetus. It can be categorized as being either symmetric or asymmetric depending on the timing of the insult during pregnancy.<sup>3</sup>

An IUGR is a clinical definition and applies to neonates born with clinical features of malnutrition and in-utero growth retardation, irrespective of their birth weight percentile.<sup>4,5</sup> The incidence of fetal growth restriction varies depending upon the population residing in the developing and developed countries with a incidence rate of 6–30% to 2–5% in these countries, respectively.<sup>6,7</sup> The highest rate of prevalence of fetal growth restriction is found in Asia, particularly in Southeast Asia, followed by Africa and Latin America.<sup>8,9</sup>

The risk factors for IUGR comprise a wide range of conditions and their assessment should be seriously taken into account, as they are easy to perform and are routinely used during pregnancy.<sup>10</sup> The main factors assessed in clinical practice include: maternal factors [socioeconomic status, weight (very low and also increased body mass index), smoking, use of recreational drugs, advanced maternal age, nulliparity, history of gestational hypertension, family history of IUGR or previous IUGR pregnancy, previous pregnancy with preeclampsia, IUFD, inherited or acquired thrombophilia, anemia, high altitude living, autoimmune disorders (phospholipid syndrome, lupus erythematosus), antepartum diabetes mellitus, chronic diseases (chronic pulmonary disease, cyanotic heart disease)], fetal factors [multiple gestation, congenital infections

(Cytomegalovirus, Syphilis, Rubella, Varicella, Toxoplasmosis, Tuberculosis, HIV, Malaria), aneuploidies (trisomy 13, 18, 21, triploidy), genetic syndromes], adnexal factors [uterine malformations, subchorionic haematoma, extensive villous infarction, marginal or velamentous cord insertion, placental mosaicism].<sup>10,11</sup>

Ultrasound is the benchmark for accurate pregnancy dating and diagnosis of FGR. However, there is room for error and FGR is undetected in about 30% of routinely scanned cases and incorrectly detected in 50% of cases.<sup>12</sup>

## Material and Methods

This study on IUGR was conducted in the Department of Obstetrics and Gynaecology of a tertiary care teaching hospital, Kolkata. Women who attended the Obstetric OPD in their 1<sup>st</sup> trimester of pregnancy and those who were thought would be able to visit the antenatal clinic for their fortnightly check-up regularly were screened for intrauterine foetal growth retardation. Women with irregular and uncertain menstrual history and where the 1<sup>st</sup> trimester USG foetal crown rump length did not corroborate with the menstrual gestational age were excluded from this study. A meticulous history was taken. Enquiry was made regarding socio-economic status, addition, contraceptive used and working habits of the pregnant women. Family history including hypertension, diabetes, twins, delivery of small for dates baby, bronchial asthma, TB, venereal diseases were noted. Menstrual history includes first date of last menstrual period, cycle, flow, duration and regularity. Obstetrical history highlighted history of abortion, stillbirth, neonatal death, previous birth weight, any complication of the mother including previous pregnancies, during and after delivery.

Assessment of period of gestation i.e. attitude, presentation of foetus, foetal heart sound were done in each antenatal visit, height of fundus and growth of abdomen in centimetres were measured from 20 and 30 weeks respectively, every

fortnightly. Routine investigation like blood for Hb in gm% in first visit and monthly for 24 weeks of pregnancy, ABO grouping and Rh typing, blood sugar in first visit, then at 28, 32, 36 weeks, uric acid, serum magnesium, serial estimation of urinary oestriol to creatinine ratio were done. Ultrasonographic obstetrical examination was done in the first trimester to confirm the gestational period and subsequently at 16, 24, 28, 32 and 36 weeks of gestation to measure the biparietal diameter, head and abdominal circumference and amount of liquor amni.

Monitoring of foetal growth was done clinically by noting the maternal weight gain, height of uterus and girth of abdomen, biochemically by urinary oestriol: creatinine ratio estimation, and biophysically by ultrasonography. Decision regarding delivery was taken in between 36-38 weeks depending on certain jeopardy of fetoplacental unit with special consideration to pediatric attention and monitoring system during labor. Patients who had bad obstetrical history, elderly, history of intertillity, uncontrolled PIH, gross foetal retardation with any risk factor were terminated by elective lower uterine caesarean section; where foetal lung immaturity was suspected prophylactic dexamethasone 4 mg i.m. inj twice daily for 3 days were given prior to induction of delivery. In rest of the patients where vaginal delivery were contemplated monitoring by adequate checking of foetal heart sound and 12hr foetal kick count were done.

After delivery sex, head and abdominal circumference, presence of foetal growth restriction i.e. weight, palm & sole crease, earlobe cartilage, absence of vernix, presence of nail till tip of finger and any congenital anomaly were noted. Fresh placenta was collected from labour room and operation theatre for early examination. The placental foetal and maternal surfaces were examined for any calcification, macroscopic infract area, blood clot, few placenta were sent for histopathological study and the umbilical cord was examined for any abnormality [Fig. 1, 2].

## Results

Total number of deliveries in 9 months study period was 1118 and total number of IUGR cases was 203 with the incidence of 18.25% of IUGR cases. Twenty five cases of IUGR thus diagnosed were taken up for this study and another 25 cases of normal pregnancy were studied as control. Present study showed 4 (16%) symmetrical and 21 (84%) asymmetrical growth retardation.

**Table 1:** Showing age distribution in IUGR and control cases

Age group	IUGR cases [n=25]	Control [n=25]
Below 19 years	4 (16%)	2 (8%)
20- 25 years	4 (16%)	12 (48%)
26- 30 years	13 (52%)	9 (36%)
31 years and above	4 (16%)	2 (8%)

Highest incidence of IUGR was among 26-30 years of age group [Table 1].

**Table 2:** Showing distribution of parity in IUGR and control cases

Age group	IUGR cases [n=25]	Control [n=25]
Primigravida	18 (72%)	10 (40%)
Second Gravida	2 (8%)	10 (40%)
Third gravida	2 (8%)	3 (12%)
Fourth garvida and above	3 (12%)	2 (8%)

Foetal growth restriction was maximum among primigravida [Table 2].

**Table 3:** Distribution of significant past and family history in IUGR and control cases

Past and family history	IUGR cases [n=25]	Control [n=25]
2 or more previous abortions	2 (8%)	1 (4%)
Infertility (Primary/Secondary)	6 (24%)	1 (4%)
Previous IUGR baby	2 (8%)	-
Family History of IUGR	2 (8%)	-
H/O of congenital malformation	1 (4%)	-
Total	13 (52%)	2 (8%)

Significant past and family history was present in 52% of IUGR cases against 8% in control [Table 3]. Significant predisposing factors in present pregnancy were detected in 64% cases of IUGR against only 4% in control. Significant past and family history was present in 52% of IUGR cases against 8% in control. Majority (44%) of IUGR

cases were found among low middle income group in the present study. Mean booking weight in IUGR group was (44.4 kgs), significantly higher than control cases.

**Table 4:** Distribution of IUGR and control cases according to socioeconomic class of family

Socioeconomic class	IUGR cases [n=25]	Control [n=25]
Low	8 (32%)	6 (24%)
Lower middle	11 (44%)	14 (56%)
Higher middle	5 (20%)	4 (16%)
High	1 (4%)	1 (4%)

Majority (44%) of IUGR cases were found among lower middle income group in the present study [Table 4].

**Table 6:** Analysis of maternal Hb level in IUGR and control cases

Gestational Week	IUGR ± Complications [n=25]			Control [n=25]		
	No. of Observations	Range	Mean	No. of Observations	Range	Mean
10-12	25	7.5-12.6	10.8	25	10.4-13.2	11.7
24-26	25	7.6-12.4	10.3	25	10.2-12.8	11
28-30	25	7.8-12.2	10.2	25	10.2-11.8	10.9
32-34	25	7.5-11.6	10.4	25	9.4-12.6	11.5
36-38	18	7.5-12.8	10.5	21	10.2-13.2	12.1

Hb level was found lower in IUGR cases than control group [Table 6].

**Table 7:** Analysis of maternal post prandial blood sugar level in IUGR and control cases (mg %)

Gestational Week	IUGR ± Complications [n=25]			Control [n=25]		
	No. of Observations	Range	Mean	No. of Observations	Range	Mean
10-12	25	68-118	98.1	25	71-123	100.5
28-30	25	70-110	91.6	25	73-122	98.7
32-34	25	66-105	85.3	25	72-121	96.8
36-38	18	63-110	83.6	21	70-116	99.4

Maternal blood sugar level was relatively low at term in IUGR group [Table 7].

**Table 8:** Analysis of maternal serum uric acid level in IUGR and control cases (mg %)

Gestational Week	IUGR ± Complications [n=25]			Control [n=25]		
	No. of Observations	Range	Mean	No. of Observations	Range	Mean
23-24	22	3-5.1	4.3	25	3.2-4.8	4.2
27-28	24	3.8-5.7	4.3	25	3.1-4.7	4.3
31-32	20	4.1-6.5	5.1	25	3-4.9	4.4
35-36	18	4.2-6.7	5.6	24	3-5.1	4.4
39-40	16	3.7-7.3	5.6	14	3.1-5	4.5

Maternal uric acid level was higher in IUGR (5.6%) than control group [Table 8].

**Table 5:** Booking weight at first trimester of pregnancy

Cases	Initial weight in Kgs	
	Range	Mean
IUGR (n=25)	35-51	44.4
Control (n=25)	39-68	51

Mean booking weight in IUGR group was (44.4 kgs) significantly lighter than control subjects [Table 5]. Total mean weight gain with treatment in IUGR group was 6.5 kgs from first visit in 1<sup>st</sup> trimester till delivery. Measurement of symphysis-fundal height showed significant difference among IUGR and control group.

**Table 9:** Analysis of 24 hrs urinary oestriol and creatinine ratio in IUGR and control cases

Gestational Week	IUGR ± Complications [n=25]			Control [n=25]		
	No. of Observations	Range	Mean	No. of Observations	Range	Mean
24-25	23	6.2-15.8	9	25	6.8-15.6	9.2
26-27	24	7.8-16.2	9.4	25	8.6-17.4	10.6
28-29	25	8.4-18	10.2	25	9.4-18.6	12.7
30-31	25	12.2-21.7	14.5	25	11.3-22.6	14.2
32-33	25	14.4-22.4	15.2	25	14.2-24	16.6
34-35	24	14.2-26.8	19.8	25	14.8-30.4	21.4
36-37	20	16.1-35.2	21.6	24	17.2-38.8	23.2
38-39	18	10.8-32.7	22	20	12.6-37.6	24.5
40-41	16	8.1-34.4	22.2	12	11.8-39.2	25.3

Maternal urinary oestriol and creatinine ratio was found to be slightly lower in IUGR group [Table 9].

**Table 10:** Analysis of ultrasonographic head circumference to abdominal circumference ratio in IUGR and control cases

Gestational Week	IUGR ± Complications [n=25]			Control [n=25]		
	No. of Observations	Range	Mean	No. of Observations	Range	Mean
16	18	0.81-0.91	0.84	25	0.8-0.88	0.83
24	22	0.83-0.99	0.90	25	0.85-0.95	0.90
28	23	0.98-1.17	1	25	0.91-0.98	0.95
32	25	1.13-1.21	1.16	25	0.87-0.98	0.93
38	23	1.10-1.21	1.14	24	0.94-1.10	0.99

IUGR became evident from 28 weeks onwards in some cases by HC:AC ratio measurement [Table 10, Fig. 5]. There was no difference of CRL in 1<sup>st</sup> trimester of pregnancy in IUGR and control cases. Difference of BPD was observed more from 28 weeks of gestation in IUGR cases. No significant

difference was observed in head circumference measurement in IUGR and Control cases. Abdominal circumference was found to be less in IUGR group than control cases from 28 weeks onwards in serial USG examination.

**Table 11:** Analysis of USG measurement of foetal femoral length [in CMs] in IUGR and Control Cases

Gestational Week	IUGR ± Complications [n=25]			Control [n=25]		
	No. of Observations	Range	Mean	No. of Observations	Range	Mean
16	18	2.3-2.6	2.53	25	2.4-2.6	2.52
24	22	4.1-4.3	4.21	25	4.2-4.3	4.25
28	23	4.5-5.1	4.85	25	4.9-5.2	5.05
32	25	5.5-6.1	5.83	25	6-6.3	6.15
36	23	5.7-6.6	6.3	24	6.9-7.1	7

Femoral length was found to be shorter in IUGR group than control cases after 32 weeks gestation [Table 11, Fig. 3, 4]. Earliest detection of oligohydramnios and suspicion of IUGR was possible at 16 weeks. Earliest diagnosis of IUGR was done at 28 weeks, but majority (64%) were diagnosed between 32-34 weeks. Caesarean section rate was 2.5 times more in IUGR group as compared to control for obvious reasons.

**Table 12:** Showing suspicion/detection of IUGR antenatally at different gestational week

Gestational week	16-20	24-26	28-30	32-33	36-38	Mode
Oligohydramnios detected by USG in IUGR group 12 (48%)	1 (4%)	1 (4%)	3 (12%)	3 (12%)	4 (16%)	36 weeks
IUGR detected n=25	-	-	3 (12%)	16 (64%)	6 (24%)	32 weeks

Earliest detection of oligohydramnios and suspicion of IUGR was possible at 16 weeks. Earliest diagnosis of IUGR was done at 28 weeks,

but majority (64%) were diagnosed between 32-34 weeks [Table 12, Fig. 6].

**Table 13:** Analysis of nature of delivery in IUGR and control cases

	Vaginal Delivery			Lower Segment Caesarean Section	
	Normal	Forceps	Ventouse	Elective	Emergency
IUGR [n=25] cases	6 (24%)	2 (8%)	-	13 (52%)	4 (16%)
Control (n=25)	13 (52%)	5 (20%)	-	3 (12%)	4 (16%)

Caesarean Section rate was 2.5 times more in IUGR group as compared to control for obvious reasons [Table 13].

**Table 14:** Analysis of placental weight of IUGR and control cases

IUGR [n=25 ] cases	<300 gms	≥300 gms	Range	Mean
IUGR [n=25] cases	16 (64%)	9 (36%)	180-600	295
Control (n=25)	-	25 (100%)	350-700	510

Mean weight of placenta of IUGR babies are significantly low as compared to control group [Table 14, Fig 4].

**Table 15:** Analysis of perinatal mortality in IUGR and control cases

	IUFD	Early neonatal death	Survival
IUGR [n=25] cases	1 (4%)	1 (4%)	23 (92%)
Control (n=25)	-	-	25 (100%)

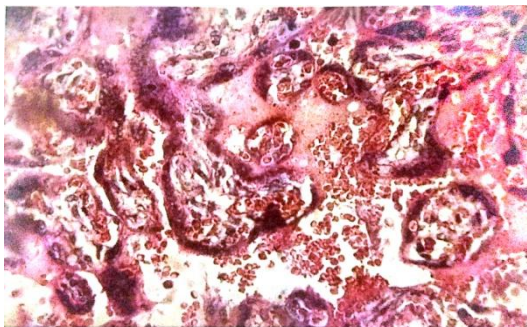
In IUGR group perinatal mortality was 8%, whereas in normal pregnancy there was no perinatal death [Table 15].



**Figure 1:** Battledore placenta found in an IUGR pregnancy



**Figure 2:** Placenta of a triplet pregnancy having IUGR



**Figure 3:** Histopathological examination shows basement membrane thickening in an IUGR pregnancy



**Figure 4:** IUGR baby weighing 1.85 Kgs along with a normal baby weighing 3.3 Kgs



**Figure 5:** Ultrasonography at 17 weeks of gestation showing abdominal circumference equivalent to 14 weeks



**Figure 6:** USG at 16 weeks 6 days gestation showing moderate oligohydramnios

## Discussion

In the present study, there is significant past and family history was present in 52% of IUGR cases against 8% in control. Highest incidence of IUGR was among 26-30 years of age group. Significant predisposing factors in present pregnancy were detected in 64% cases of IUGR against only 4% in control. Significant past and family history was present in 52% of IUGR cases against 8% in control. Majority (44%) of IUGR cases were found among low middle income group in the present study. Mean booking weight in IUGR group was (44.4 kgs), significantly higher than control cases. Fikree<sup>13</sup> and Berendes<sup>14</sup> 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.<sup>15</sup> 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.<sup>16</sup> and Odiba et al.<sup>17</sup> 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.

Hb level was found lower in IUGR cases than control group. Maternal blood sugar level was relatively low at term in IUGR group. Mansour et al. (2002)<sup>18</sup> found that maternal work was associated with low birth weight and mothers with infants who had LBW were more likely to be more than 35 years old. Parker et al. (1994)<sup>19</sup> found that maternal education, father education and maternal work were associated with low birth weight. Sharon and Gilberto (2003) found that mothers with infants who had IUGR were more likely to have less than a high school education and to be younger than 20 years.<sup>20</sup> There was no significant relationship between weight gain during pregnancy and IUGR in this study. T.

Aghamolaei et al<sup>21</sup> study supports the result of Sharon and Gilberto (2003). Mansour et al. (2002)<sup>18</sup> found that anemia is associated with low birth weight.

USG is a very important investigation in diagnosis and monitoring of IUGR. BPD was found to lag behind in IUGR group than that of control group from 28 weeks onwards in the present study. The head circumference followed the same pattern of growth like BPD in both IUGR and normal group. The present study corroborates with the findings of Campbell (1971).<sup>22</sup> Significant decrease in abdominal circumference was observed in the present study in the IUGR group it was 26.4 cms at 36 weeks when compared to control group of normal pregnancies (32.5 cms); whereas earliest difference was observed at 28 weeks, it became significant at 32 weeks. This observation correlates well with the findings of Chitty LS et al (1994)<sup>23</sup>, who could diagnose 87% of IUGR at 32 weeks by USG abdominal circumference alone.

Vaginal delivery were conducted in 32% of the IUGR cases and lower segment caesarean section in 68%, out of which 52% were delivered electively, in control group there were only 12% elective caesarean sections. In the present study only 4 babies (16%) were of less than 2 Kgs weight, out of which 2 (50%) died and survived 50%. In IUGR group majority (64%) of placenta were below 300 gms, with mean weight of 295 gms, whereas control group had mean placental weight of 510 gms, which conforms with the observation of Fox (1981).<sup>24</sup>

Of the biochemical methods uric acid level was found to be higher in IUGR group and near term, which reflects abnormal renal function and has got a bearing in weight gain of pregnant women and also as an effect of a poorly functional fetoplacental unit; there is intra uterine foetal growth retardation. Blood sugar level in the 3<sup>rd</sup> trimester were found to be low- indicating chronic hypoglycaemic state in growth retarded foetus. Urinary oestriol was found to be inconclusive alone, as a diagnostic or prognostic investigation because different laboratory has got different

standard and methodology of estimation. So combination of urinary oestriol with clinical assessment and USG gives an obstetrician immense help in finding the solution of problems so far termination and antenatal management is concerned.

USG investigation were found to be of much value when it is done serially in a methodical way at 16-20, 28-30, 32-34 and 36-38 weeks preferably by a sinologist with obstetrical background, which minimise aberrant reporting. In this study ultrasonographic abdominal circumference and HC/AC ratio were found to be of immense importance in monitoring foetal growth retardation.

In the present study, IUGR became evident from 28 weeks onwards in some cases by HC:AC ratio measurement. There was no difference of CRL in 1<sup>st</sup> trimester of pregnancy in IUGR and control cases. Difference of BPD was observed more from 28 weeks of gestation in IUGR cases. No significant difference was observed in head circumference measurement in IUGR and Control cases. Abdominal circumference was found to be less in IUGR group than control cases from 28 weeks onwards in serial USG examination. Sonography can be used to determine head-to-abdomen circumference ratio (HC/AC) to differentiate growth-restricted fetuses.<sup>25</sup> 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.<sup>26</sup> Whereas, asymmetrical growth restriction had late-onset growth failure, a low ponderal index, brain sparing and increase risks for Perinatal asphyxia and neonatal hypoglycemia.<sup>26</sup>

Vaginal delivery were deliberately avoided in marked growth retardation fetuses with



oligohydramnios and best possible assistance was planned so far deliveries were concerned and elective caesarean section rate was found to be 52% and a further 16% emergency caesarean section were done in IUGR group, in comparison to control group had only 12% caesarean section. The obstetrical outcome in the present series was 8% perinatal mortality in IUGR group and no catastrophe in the control group. In 16% of foetal growth retarded cases babies had birth weight of more than 2.5 Kgs and further 68% babies were between 2-2.5 Kgs weight. 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.<sup>27</sup> The worst outcomes are observed in severe IUGR cases, with extreme prematurity and very low weight, who present important deterioration in umbilical flow.<sup>28</sup> Bernstein et al.<sup>29</sup> 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.<sup>30</sup> 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.

### Conclusion

Foetal growth retardation was found to be double among primigravids, teenage and women above 30 years. In this study ultrasonographic abdominal

circumference and HC/AC ratio were found to be of immense importance in monitoring IUGR. In this study earliest suspicion by detecting oligohydramnios at 16 weeks were possible by USG, otherwise early diagnosis of growth retardation was done at 28-30 weeks of gestation, by and large IUGR was diagnosed clinically by measuring the fundal height, and by detecting remarkable less amount of liquor. Female babies were found to be more (68%) among IUGR series. Placenta in IUGR group was significantly lighter in weight than the control group. Measures to reduce the incidence of IUGR should include the establishment of public policies that are properly directed during pregnancy health check-up.

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