PERINATAL OUTCOME OF EARLY PRETERM STAGE II IUGR AT TWO HOSPITALS IN ADDIS ABABA: A RETROSPECTIVE CROSS SECTIONAL STUDY

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ABSTRACT

BACKGROUND: Intrauterine growth restriction is a common obstetric complication. Based on the severity, it is classified into stages 0-IV. Stage II IUGR is defined as ultrasound estimated fetal weight less than 10th percentile for gestational age with absent end diastolic velocity on umbilical artery Doppler ultrasound. Studies focusing on perinatal outcome of specific class of IUGR are limited.

OBJECTIVE: The aim of this study was to show the magnitude of stage II IUGR and see the perinatal outcome of early preterm stage II IUGR at two public hospitals in Addis Ababa, Ethiopia.

METHOD: A retrospective cross sectional study was conducted from January 2019 to August 2022. Data was collected from medical records using a structured pre-tested questionnaire. The data was coded, entered, and analyzed using SPSS version 25.

RESULT: There were 49,338 deliveries at the two study hospitals. Of these 192 pregnancies were complicated by stage II intra uterine growth restriction; 151 of which were diagnosed at the early preterm gestational age. The prevalence of stage II IUGR was 0.39% while the prevalence of early preterm stage II intra uterine growth restriction was 0.3% out of the total deliveries. Preeclampsia was the leading obstetric complication diagnosed in 107 (70.9%) of the cases. Mode of delivery for all of the neonates was by cesarean section and all required neonatal intensive care unit admission. The single most common perinatal morbidity was respiratory distress, which accounted for 42 (27.8%) of the cases. Half of the 151 pregnancies diagnosed with early preterm stage II intrauterine growth restriction, 75 (50 %), ended up in perinatal death. The majority of the perinatal losses were during early neonatal period, 56% (42/75). Compared to those with birth weight of <1000gm, those with birth weight of 1500-2499gm had more than 37 times chance of survival in the perinatal period (AOR=37.67 (7.05, 201.36), p<0.000).

CONCLUSION: The prevalence of stage II IUGR was 0.39% whereas the prevalence of early preterm stage II IUGR was 0.3%. Early preterm stage II IUGR was associated with significant perinatal morbidity and mortality. Birth weight was a determinant factor significantly associated with perinatal survival.

KEY TERMS: IUGR, Stage II IUGR, perinatal death, perinatal outcome.

(The Ethiopian Journal of Reproductive Health; 2023; 15;1-10)

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INTRODUCTION

Intrauterine growth restriction (IUGR) is a complex syndrome characterized by fetal growth defect that leads to failure to achieve the genetically determined growth potential.[1] Several international professional organizations define IUGR as ultrasound estimated fetal weight less than the 10th percentile for the gestational age.[2] IUGR is a common obstetric complication affecting 5-10% of pregnancies. The highest incidence of IUGR was reported in South Central Asia, where it accounts for about 33%.[3] In Ethiopia, there are few studies done on IUGR in general and IUGR with specific Doppler abnormality in particular. In a hospital based cross sectional study conducted in South Gondor, IUGR prevalence was 23 %.[4] The prevalence of IUGR with severe UA Doppler abnormality (absent or reversed end diastolic (A/RED) velocity), i.e. stage II or stage III IUGR, is even rarer and is about 2.13%.[5]

The etiology of IUGR is diverse and overlapping and the pathophysiology is complex. The underlying cause can be due to maternal medical or obstetric complications, fetal condition, placental disease or the overlap of these.[2, 6] Fetal causes of IUGR include structural and chromosomal abnormalities, fetal infection, and exposure to drugs-both prescription and drugs of abuse.[2, 6]

Ultrasound has become the most essential tool in the diagnosis and growth monitoring of fetuses with IUGR. Doppler ultrasound specifically has revolutionized the diagnosis and management of fetal growth restriction. Doppler ultrasound of fetal vessels is used for a stage-based classification of fetal growth restriction based on the severity of the Doppler abnormality. It therefore helps guide timing of delivery and prediction of outcome. Accordingly, fetal growth restriction is classified into five stages based on Doppler abnormality.[7]

Stage 0 IUGR: EFW<10th percentile with normal Doppler

Stage I IUGR: EFW<3rd percentile OR EFW<10th percentile with UA PI>95th percentile

Stage II IUGR: EFW<10th percentile and AEDV on UA Doppler study

Stage III IUGR: EFW<10th percentile and REDV on UA Doppler study

Stage IV IUGR: EFW<10th percentile with reversed diastolic flow of ductus venosus (DV) or pathologic CTG

Studies have confirmed that the perinatal outcome of growth-restricted fetuses with underlying placental disease highly correlates with the degree of Doppler abnormality.[8, 9]

IUGR is one of the most common causes of perinatal morbidity and mortality. Perinatal mortality and morbidity is high for stage II IUGR and above, compared to stage 0 or stage I IUGR. Preterm delivery is also more common among those with A/RED velocity of umbilical artery Doppler ultrasound.[5, 10-12] The adverse perinatal outcome is even worse in early onset disease, i.e. when it is diagnosed before 32 weeks of gestation.[13, 14] Perinatal outcome of IUGR with AEDV of umbilical artery Doppler is poor. Perinatal outcomes such as APGAR score at 1 min below 4, use of a ventilator, admission to the neonatal intensive care unit (NICU), respiratory disease, neurologic disease, neonatal sepsis, anemia, thrombocytopenia, and neonatal mortality were statistically less favorable in the AEDV group compared to those in the control group independent of gestational age and presence of oligohydramnios.[15] In addition, long-term health consequences are also considerable. Low birth weight caused by IUGR was known to be associated with increased rates of cardiovascular disease and noninsulin-dependent diabetes in adult life.[16]

Prenatal screening, early diagnosis, surveillance and timing delivery based on antepartum test result are the only strategies currently available in the management of intrauterine growth restricted fetuses. Antepartum surveillance with fetal BPP and Doppler ultrasound has been the mainstay of the management of these pregnancies in guiding either delivery or expectant management. Particularly important is Doppler study of ductus venosus as it

predicts perinatal outcome and time delivery in early intrauterine fetal growth restriction.[17] Early onset IUGR poses a great challenge of management.[18,19] There is lack of consensus regarding mode and the timing of delivery.[20-22] The high likelihood of disease progression and fetal deterioration necessitates intervention, whereas early delivery increases perinatal mortality. This requires adequate data on perinatal outcome of IUGR with respective Doppler abnormalities. Perinatal outcome of stage 0 and stage I IUGR is slightly higher but comparable with pregnancies without IUGR. On the other hand, pregnancies with stage III and above have the worst perinatal outcome. Stage II IUGR is a gray area as to the antepartum management, time of delivery, and perinatal outcome.[23] Studying perinatal outcome of specifically stage II IUGR may be helpful in providing information that can contribute to guideline development for the management of this cohort.

Controversies continue until strong evidence is available to guide the management of IUGR with AEDV. Studies on perinatal outcome of stage II IUGR are limited in the local context. This study will contribute in this regard by demonstrating the perinatal outcome of early preterm IUGR with AEDV of the UA. The purpose of this study is to show the magnitude and perinatal outcome of early preterm (28-34weeks of gestation) stage II IUGR in the set up of two public hospitals in Addis Ababa, Ethiopia.

METHODS

This was a facility based cross sectional study conducted at two government teaching hospitals in Addis Ababa, Ethiopia; namely Tikur Anbesa Specialised Hospital (TASH) and Gandhi Memorial Hospital (GMH). The study period was from January 2019 to September 2022.

Inclusion criteria: EFW<10th percentile and AEDV of UA Doppler study, singleton intrauterine pregnancy, early milestone confirmed gestational age, gestational age from 28-33+6 weeks at diagnosis, cesarean delivery, patients for whom complete pertinent information is obtained.

Exclusion criteria: multiple gestation, structural congenital anomalies, chromosomal anomalies, congenital intrauterine infection, EFW< 10th percentile but normal UA Doppler umbilical arterial Doppler abnormality other than AEDV, unknown gestational age, vaginal delivery, IUFD before IUGR is confirmed by Doppler study, incompletely documented patient information.

Independent variables: Maternal socio-demographic variables were age, marital status, religion, educational status and occupation. Obstetric variables included parity, GA at diagnosis, administration of medications magnesium sulfate & dexamethasone and obstetric complications. Obstetric complications included ante-partum hemorrhage (APH), preeclampsia, eclampsia, preeclampsia with HELLP syndrome, HELLP syndrome and others. Medical variables included complications that were diagnosed and grouped into chronic hypertension, cardiac disease, diabetes mellitus, chronic renal disease, and others.

Dependent outcomes/variables: Progress of disease to stage III or stage IV, antepartum intrauterine fetal death, intrapartum fetal death, Gestational age at delivery, APGAR score, need for neonatal resuscitation, perinatal mortality, perinatal morbidity, birth weight and discharge outcome at the end of the 1st week of post natal life.

Sampling procedure: According to the health management information system (HMIS) of the two hospitals, 49,338 deliveries took place from 2019 to 2021. Stepwise approach was followed to know the final sample size by using labor and delivery room registration books, OR registration books, ward admission & HMIS books and patient medical record. Initially, all cesarean deliveries and stillbirths of birth weight of ≤ 2500gm were screened from the labor ward registration book and 701 cases were identified. Of these 188 were stillbirths. Thereafter ward and OR registration books were reviewed by looking for patients admitted with the diagnosis

of stage II IUGR and those delivered by C/S for stage II IUGR or indications like NRBPP, HELLP syndrome or placental abruption. Subsequently, we identified 436 cases. The medical records of these 436 cases and stillbirths were reviewed to identify early stage II IUGR. At this stage, 192 cases managed for stage II IUGR were identified from which 41 were excluded because they did not fulfill the inclusion criteria and hence the final sample size was 151.

Data collection: A structured pre-tested questionnaire prepared in English was used to collect data from the patient medical record and NICU registration books. Data was collected from the time of admission to maternity ward when the patients were discharged from the hospital or 7th day postpartum, whichever comes first. Data was collected by researcher from the data source with cooperation from the staff at record offices, wards, OR, and NICUs of the two hospitals. All data sources were assessed through a stepwise approach to include all cases that fulfilled the inclusion criteria.

Data analysis: The collected data was coded, cleaned and analyzed using statistical package for social science version 25. Chi-square test of independence was done using the primary dependent variable (PND) as a dichotomous variable (yes and no). Bivariate regression analysis was conducted for independent variables with chi-square value of <0.05. Multiple regression analysis was then employed to those variables with P-value of <0.2 on bivariate analysis. Odds ratio (OR) with their 95% confidence intervals were computed to identify the presence and strength of association, and statistical significance was declared if $p < 0.05$. Descriptive statistics and summary tables were used to describe the study findings.

RESULT

Socio demographic variables:

A total of 49,338 deliveries took place from January 2019 to December 2021 at the two hospitals: TASH and GMH. Out of these 192 pregnancies were complicated by stage II IUGR and of these 151 were diagnosed at the early preterm gestational age. Hence, the prevalence of stage II IUGR was 0.39% whereas the prevalence of early preterm stage II IUGR was 0.3% out of the total deliveries.

The age of the majority of the mothers, 67 (43.4%), was in the range 26-30 years. There was no participant mother younger than 18 years. Nearly all the mothers, 149 (98.7%), were married. One hundred six (70.2%) were orthodox in religion followed by 35 (23.2%) Muslims. Sixty (39.7%) of the mothers have completed preparatory school. Higher education graduates accounted for 42 (27.8%) of the cases. Majority of the mothers, 82 (54.3%), were housewives and 41 (27%) were government employees. (Table 1)

Table 1: Socio-demographic characteristics of pregnant women managed for stage II IUGR.

Socio-demographic factor		Frequency	%
Maternal age in years	18-25	50	33.1
	26-30	67	43.4
	31-35	17	11.3
	>35	17	11.3
Marital status	Single	2	1.3
	Married	149	98.7
Religion	Orthodox	106	70.2
	Muslim	35	23.2
	Protestant	10	6.6
Educational status	Illiterate	8	5.3
	Up to grade 10 completed	41	27.2
	Preparatory completed	60	39.7
	Higher education	42	27.8
Occupation	Housewife	82	54.3
	Daily laborer	3	2
	Merchant	25	16.6
	Government employee	41	27.2

Maternal reproductive and obstetric characteristics

Nearly two-third, 90 (59.6%), were nulliparous. Multi-para (para1-4) and grand multiparity (para ≥5) accounted for 38.4% (58/151) and 2% (3/151) respectively. The majority of the diagnosis of stage

II IUGR, 81 (53.6%), was made at GA of 32-34 weeks whereas the rest 70 (46.4%) were diagnosed between 28-32 weeks of gestation. Majority, 131 (86.8%) had no chronic medical diseases. Cardiac diseases and chronic hypertension were identified in 7 (4.6%) and 4 (2.6%) of the cases respectively. Pre-gestational diabetes mellitus and chronic renal disease each complicated 2 (1.3%) of the cases. The remaining 5 (3.3%) of the cases were complicated by various medical complications like HIV, epilepsy etc. (Table 2)

Table 2: Maternal reproductive and obstetric variables of pregnant women managed for early preterm stage II IUGR

Maternal obstetric characteristics		Frequency	%
Parity	Nulliparous	90	59.6
	1 – 4	58	38.4
	≥5	3	2
Gestational age II IUGR at diagnosis of stage	28-32	70	46.4
	32-24	81	53.6
Medical complications	Chronic hypertension	4	2.6
	Cardiac disease	7	4.6
	Diabetes	2	1.3
	Renal disease	2	1.3
	Other (HIV, epilepsy, etc.)	5	3.3
	none	131	86.8

Preeclampsia was the leading obstetric complication diagnosed in 107 (70.9%) of the cases. In 18 (11.9%) of the cases preeclampsia with HELLP syndrome was diagnosed. On the other hand, HELLP syndrome complicated 6 (4%) of the cases. Ante-partum hemorrhage (APH) and eclampsia each complicated 1 (0.7%) of the cases. The remaining 15 (11.9%) of the cases grouped under 'other' were complicated by APH, oligohydraminios, preterm pre-labor rupture of the membranes or no any identifiable obstetric complication.

Majority of the participants, 101 (66.9%), were provided both magnesium sulfate and dexamethasone antenatally for seizure prophylaxis and/or fetal neuro-protection. Seven (4.6%) of the cases were provided only dexamethasone. In 2 (1.3%) of the cases, only magnesium sulfate was administered for seizure prophylaxis. In 41 (27.2%) of the cases, however, none of these medications were provided.

Perinatal outcome:

Out of the 151 pregnancies complicated by stage II IUGR; 14 (9,3%) and 2 (1.3%) progressed to stages III and stage IV IUGR respectively. Of these 11/16 were diagnosed between the GA of 28-32 weeks and the remaining 5/16 were diagnosed between the GA of 32-34. Therefore, these 16 cases were excluded from the analysis of the perinatal outcome. There were 32 (21.2%) antepartum fetal losses. One case (0.7%) entered into labor while on inpatient management and fetus died before delivery. Hence, 102 babies were delivered alive as stage II IUGR.

Eighty four (55.6%) of the neonates were delivered between the GA of 32-34 weeks whereas 37 (24.5%) were delivered between the GA of 28-32 weeks and only 14 (9.3%) were delivered after 34 completed weeks. There was no report of presence of intra-op meconium. Overall 22 (14.6%) and 9 (6%) neonates had low first and fifth minute APGAR scores respectively. Ten (6.6%) of these required resuscitation with bag and mask ventilation. All of the neonates were admitted to the NICU. The birth weight of the neonates was 1500-2449 and 1001-1449 grams in 41 (27.2%) and 56 (37.1%) of the cases. The extremely low birth weight (<1000 grams) group accounted for 38 (25.2%) of the cases. The single most common perinatal morbidity was RDS, which accounted for 42 (27.8%) of the cases, followed by sepsis with RDS which accounted for 31 (20.5%) and sepsis alone, which accounted for 19 (12.6%). IVH was diagnosed in 3 (2%) of the neonates and in 5 (3.3%) neonates RDS, NEC, IVH, sepsis, & hyperbilirubinemia were co-morbid. NEC and Hyperbilirubinemia each accounted for 1 (0.7%) case. No neonate was diagnosed with electrolyte abnormality and MAS.

Half of the 151 cases diagnosed with early preterm stage II IUGR, 75 (50 %), ended up in perinatal death. Majority of the perinatal losses was during early neonatal period (ENND), 56 % (42/75). Only 21 (13.9%) of the neonates that were discharged improved within the 1st week of postnatal period and 39 (25.8%) stayed in the NICU beyond the 1st week of life. (Table 3)

Table 3: Summary of the perinatal outcome of pregnant women managed for early preterm stage II IUGR

Perinatal outcome		Frequency	%
Disease progression (n-151)	To stage III IUGR	14	9.3
	To stage IV IUGR	2	1.3
	No progress	135	89.4
Antepartum IUFD	Yes	32	21.2
	No	103	68.2
Gestational age at delivery	28-32	37	24.5
	32-34	84	55.6
	>34	14	9.3
Intra partum IUFD	Yes	1	0.7
	No	102	67.5
Presence of meconium	Yes	-	-
	No	102	67.5
1st minute APGAR	<7	22	14.6
	≥7	80	53
5th minute score	<7	9	6
	≥7	93	61.6
Need for resuscitation	Yes	10	6.6
	No	92	60.9
Birth weight in grams	≤1000	38	25.2
	1001-1449	56	37.1
	1500-2449	41	27.2
Admission to NICU	Yes	102	67.5
	No	-	-
Diagnosis at NICU	RDS	39	25.8
	Sepsis	19	12.6
	RDS, sepsis	31	20.5
	RDS, NEC, IVH, sepsis, hyperbilirubinemia	10	6.6
Discharge outcome	Died within the 1st 7 days	42	27.8
	Stayed beyond the 1st 7days	39	25.8
	Discharged improved within the 1st 7 days	21	13.9

Factors associated with Perinatal Death

A stepwise analysis was done to look for potential association between the independent variables and perinatal death. Variables (factors) which were associated with PND in the bivariate logistic regression analysis ($P < 0.05$) were maternal age, GA at diagnosis, obstetric complications and birth weight. After adjusting for potential co-founders in multivariate logistic regression analysis, only birth weight remained to be significantly associated with PND ($P < 0.05$).

Compared to those with birth weight of <1000gm, those with birth weight of 1500-2499gm had more than 37 times chance of survival in the perinatal period (AOR=37.67 (7.05, 201.36), p<0.000). When stage II IUGR was diagnosed between the GA of 32-34 weeks, chance of perinatal survival was 3.9 time higher (95% CI 1.97, 7.61, p<0.001) than when the disease was diagnosed at 28-32 weeks GA, although the association is lost in multivariate analysis. This means very early onset disease is likely to be associated with increased perinatal mortality. Similarly, early preterm stage II IUGR that has an onset later than 32 completed weeks is less likely to worsen when compared to 28-32 week, although not statistically significant.

Table 4: Bivariate and multivariate logistic regression of neonatal outcome of pregnant women managed for early preterm stage II IUGR.

Predictor variable	Frequency	Perinatal death (PND)		p-value	COR with 95%CI	P-value	AOR with 95%CI
	Yes	no					
Maternal age							
• 18-25	50	27	23	1		1	
• 26-30	67	34	33	0.164	1.14 (0.54, 2.37)	0.508	0.71 (0.25, 1.97)
• 31-35	17	4	3	0.036*	3.82 (1.09, 13.33)	0.630	1.49 (0.29, 7.69)
• >35	17	10	7	0.730	0.82 (0.27, 2.51)	0.984	0.98 (0.79, 5.93)
Gestational age at diagnosis							
• 28-32	70	47	23		1		1
• 32-34	81	28	53	0.000*	3.87(1.97, 7.61)	0.134	2.16 (0.79, 5.93)
Obstetric complication							
• Preeclampsia/ Eclampsia	108	50	58		1		1
• HELLP syndrome	6	5	1	0.114	0.17 (0.02, 1.53)	0.458	0.42 (0.04, 4.25)
• Preeclampsia with HELLP syndrome	18	15	3	0.008*	0.172 (0.47, 0.63)	0.346	0.42 (0.07, 2.57)
• Others	16	4	12	0.119	2.59 (0.78, 8.53)	0.081	4.54 (0.83, 24.74)
Birth weight							
• ≤1000gm	38	35	3		1		1
• 1001-1449gm	56	33	23	0.001*	8.13 (2.23, 0.29.65)	0.010*	7.12 (1.61, 31.41)
• 1500-2499gm	41	7	34	0.000*	56.67 (13.53, 237.4)	0.000*	37.67 (7.05, 201.36)

* p<0.05

DISCUSSION

This study showed that the overall prevalence of stage II IUGR was 0.39% (192/49,338) and the prevalence of early preterm (28-34 weeks of gestation) stage II IUGR was 0.3% (151/49,338) respectively. There are limited studies worldwide on the prevalence of stage II IUGR i.e. IUGR with AEDV. A systematic review conducted by Vogel et.al.5 showed the prevalence of both IUGR with either AEDV or REDV to range from 0.08%-2.13% among different populations. The result of this study is, therefore, comparable to their findings. Another study done in Uganda revealed that the prevalence of IUGR with AEDV among 155 pregnant women who had preeclampsia was 7.7%.24 This high prevalence may be due to the high risk of utero-placental insufficiency due to abnormal placental vascular development in this particular population.

Hypertensive disorders of pregnancy, particularly preeclampsia, were the most common obstetric complication identified in this study. This is an evidence for utero-placental cause of IUGR. Studies conducted by P. Gimei etal. and Kirsten GF etal. showed similar results.[24, 25] Another study done in Korea also found that hypertension was the most common obstetric and medical complication in pregnancies complicated by stage II IUGR.[15]

According to this study, the earlier the GA at which stage II IUGR was diagnosed, the more likely was it to progress to the Doppler abnormality i.e. stages III and IV IUGR. This leads to early intervention to deliver the fetus, which itself contributes to poor perinatal outcome. This finding is similar to what was found by O. M. Turan et al. in their study.[19] Indicated preterm delivery due to deteriorating fetal condition is most common in pregnancies with early onset disease, particularly before 30 weeks of GA.

This early intervention can itself be a contributor to poor neonatal outcome. Another indicated early delivery is for maternal indication because of co-morbid obstetric and medical complications, which is the case in this study. Studies done in Sweden and Germany revealed that indicated early delivery in early onset disease is associated with poor perinatal outcome.[18, 23] Ahmet also confirmed this by his systematic review that fetal growth restriction that onset before 34 weeks of gestation is associated with indicated early delivery, significantly lower survival rate, and increased perinatal morbidity.[26] All of these findings are consistent with the result of this study.

The most common perinatal morbidity in this study was RDS followed by sepsis, and co morbidity of RDS and sepsis. A local study by Tolu et al. revealed a similar result where newborns with abnormal UA Doppler studies were 2.3 times more likely to develop RDS compared to those with normal UA Doppler studies.[12] Other studies conducted in Germany and Uganda had similar results.[12, 13, 18] According to this study the perinatal mortality (fetal death and early neonatal death) of early preterm stage II IUGR was 49.7%. This is comparable with the finding of a study by Wang et al. which showed a perinatal mortality of 40% in stage II IUGR.[27] Another study done in Ethiopia at St. Paul hospital found that perinatal mortality among growth restricted fetuses with abnormal umbilical artery Doppler indices (elevated PI, AEDV and REDV) was 24.3%.[12] The difference may be due to their small sample size and their study of course included both AEDV and REDV.

CONCLUSION AND RECOMMENDATIONS:

The prevalence of stage II IUGR in the present study was 0.39% whereas the prevalence of early preterm stage II IUGR was 0.3%. This study showed that early preterm stage II IUGR is associated with significant perinatal morbidity and mortality. It also showed that hypertensive disorder of pregnancy is the commonest obstetric complication associated with IUGR. Birth weight was the only significantly associated factor which determined perinatal survival. This study can serve as a baseline for future studies on the same topic and on this specific population. To better understand the perinatal outcome of early preterm stage II IUGR and guide protocol development for its management, future large-scale prospective studies are recommended.

DECLARATIONS

Limitations: The main limitation of this study is being retrospective as there is a chance of missing some cases. In addition, due to the small sample size it was difficult to see the effect of each independent variable on the outcome variables.

Acknowledgement

We would like to thank TASH department of obstetrics and gynecology and department of pediatrics, specially the NICU and GMH for their unreserved cooperation, which enabled us collect all the necessary data and information.

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