ORIGINAL ARTICLE

Liver Dysfunction in Pregnancy as a Maternal Factor in the Causation of Stillbirth: A Single Center Experience

Harsha S Gaikwad[1], Kashika Nagpal[2], Banashree Nath[3], Poornima Sharma[4], Pratima Mittal[5], Achla Batra[6]

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Abstract

Background and aim: Liver disorder is relatively rare in pregnancy and its association with stillbirths has not been much investigated. We undertook the index study to find the incidence of stillbirth in pregnant women with liver disorders and to compare the maternal characteristics in pregnant women with liver disorders delivering live births.

Methodology: Retrospective data from 3 years were extracted from the neonatal–perinatal database encompassing the stillbirth registry. All pregnant women who had stillbirths, with preexisting or diagnosed as having a liver disorder during the index pregnancy were included for analysis.

Results: The incidence of stillbirths due to liver disorder in pregnancy was 4.4%. There was a significant difference between the two groups of women with liver disorders delivering stillbirths and livebirths in terms of the number of antenatal visits [$p < 0.05$, odds ratio (OR) = 2.43 (1.47–4.03)], the incidence of hypertension of pregnancy [$p = 0.026$, OR =1.94 (1.07–3.53)], and abruption [$p < 0.05$; OR = 7.9 (4.09–15.24)]. Women who delivered stillbirths had higher odds of fetal growth restriction [$p = 0.058$; OR = 2.03 (0.97–4.27)], acute fatty liver of pregnancy (AFLP) [$p < 0.05$; 100 (10.75–1000)], hepatitis E virus (HEV) infection [$p < 0.05$; 3.58 (2.02–6.33)] and jaundice [$p <0.05$; 2.60 (1.50–4.51)].

Conclusion: The incidence of stillbirths due to liver disorders in pregnancy was 4.4%. Hypertension of pregnancy, abruption, fetal growth restriction, and low birth weight were significantly associated with stillbirths. Among all hepatic disorders, jaundice due to medical disorders and HEV were found significantly high in women with stillbirths.

Keywords: Incidence, Jaundice, Liver diseases, Pregnancy, Stillbirths.

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Background

A baby who dies after 28 weeks of pregnancy, but before or during birth, is classified as a stillbirth.[1] There are innumerable factors that contribute to the occurrence of stillbirths with infection scoring the highest accounting for 50% in developing countries.[2] Liver disorders in mothers are a threat to the fetus sometimes causing *in utero* fetal death but unfortunately, the subject is not quite widely investigated.

Approximately 3% of women who are pregnant are inflicted with one or the other form of liver disease with some of them causing fatality for both the mother and child.[3] The condition poses a difficult challenge to obstetricians with a wide spectrum of causes that may precipitate liver dysfunction. These disorders may be unique to pregnancy, such as hyperemesis gravidarum, intrahepatic cholestasis of pregnancy (IHCP), and preeclampsia-associated hepatic impairment, specifically hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome or not related to pregnancy like viral hepatitis, jaundice due to hemolysis, drug-induced hepatitis, and other conditions.[4]

Maternal death of 0–25% have been reported in mothers with liver disorders specific to pregnancy and the prognosis is guarded by the cause of liver disease, the extent of damage causing derangement of the synthetic, metabolic, and excretory function of the organ and the delivery timing.[5,6] Since the incidence of such organ involvement is rare in pregnancy, the research into the fetal survival and prognosis has not been investigated in detail. Hence, we undertook the index study to find the incidence of stillbirth in pregnant women with liver disorders. We also aim to compare the maternal characteristics in pregnant women with liver disorders who had stillbirths with those delivering livebirth babies.

[1,2,4,6]Department of Obstetrics and Gynaecology, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India

[3]Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Raebareli, Uttar Pradesh, India

[5]Department of Obstetrics and Gynaecology, Amrita Medical College, Faridabad, Haryana, India

Corresponding Author: Banashree Nath, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Raebareli, Uttar Pradesh, India, Phone: +91 9717492795, e-mail: nathbanashree@gmail.com

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Methodology

The study was undertaken in the Department of Obstetrics and Gynecology of a tertiary hospital in Northern India for a period of 3 years from January 2018 to December 2021. Retrospective data for the said period of 3 years was extracted from the neonatal–perinatal database encompassing the stillbirth registry. All pregnant women

who had stillbirths, with preexisting or diagnosed as having a liver disorder during the index pregnancy were included. Preexisting liver disease was diagnosed from history and/or records suggestive of organ involvement. *De novo* liver disorders were diagnosed from history and investigations advised in the present pregnancy. Maternal details were recorded in the format for stillbirth approved by WHO as a part of the stillbirth registry in the hospital. The maternal parameters studied were the epidemiology, symptoms, familial history, association of obstetric complications of pregnancy, liver function test, mode of delivery, and type of stillbirth.

The release of various enzymes, effects due to hemodilution, and alteration in coagulation profile during pregnancy bring with it changes in reference values of the biochemical and hematological tests. The liver function tests too have altered normal range during pregnancy and hence the interpretation needs modification in the event of liver disorders during this period. Liver disorders in pregnancy in our study were diagnosed in accordance with the pattern of tests laid down by Walker I et al.[7]

Results

The total number of deliveries during the 3-year period was 75,277 and there were 2,309 stillbirths in total during this period. Among the various causes of stillbirths, there were 102 cases of stillbirths associated with maternal liver disorders. Hence, the incidence of stillbirths due to liver disorders in pregnancy was 4.4% (102/2,309). Figure 1 depicts the flowchart for the selection of cases in the index study.

There was a total of 3,538 women who reported to our institution with liver disorders in pregnancy. Among them, 102 mothers delivered stillborn babies and the rest 3,436 delivered live births. The epidemiological profile of these two groups of mothers with liver disorders is presented in Table 1. A significant difference in the booking status of women was found between those with livebirths and stillbirths and hence the number of antenatal visits too. The women with stillbirths had a significantly longer period of loss of fetal movement (LOFM). A significantly higher incidence of hypertension during pregnancy and abruption was found in mothers with stillbirths. An obstetric complication of fetal growth restriction and hence low birth weight of the baby was found significantly high in mothers with stillbirths. The liver enzymes were significantly high in women with stillbirths. When considering the diagnosis of liver affliction, IHCP was found to have a better prognosis with the delivery of more live births. Acute fatty liver of pregnancy (AFLP) and hepatitis E virus (HEV) infection were associated more with women delivering stillborn babies. Jaundice due to different causes was also found in higher numbers in women with stillbirths. A significantly higher birth weight of liveborn babies was noted. The proportion of women with individual causes of liver disorders delivering stillbirths and livebirths is presented in Figure 2.

Discussion

Stillbirth is a grave tragedy that affects innumerable women and families across the globe. The status of antenatal care in a given region is reflected in the average values of this tragic parameter. India reported an impressive improvement in declining numbers of maternal and child mortality over the last decade but the stillbirth rate still remains high with an average rate of 12.4 (3.7–22.5) according to National Family Health Survey (NHFS) 2019–2020.[8]

Our retrospective study revealed that the incidence of stillbirths due to liver disorders in pregnancy is 4.4%. Pregnancy-specific causes were found in 2,875 (81.26%) of patients while pregnancy non-specific causes were found in rest (18.74%).

Intrahepatic cholestasis of pregnancy is the most common pregnancy-specific hepatic disorder found in our study. We discovered that women who delivered stillborn babies had lower odds of IHCP [odds ratio (OR): 0.54; 95% confidence interval (CI): 0.36–0.80] compared to women with live births. Furthermore, IHCP has a relatively guarded prognosis in pregnant women with a proportional relationship to maternal serum bile acid levels.[9,10] Although it is postulated that the risk of stillbirths rises with bile acids increasing beyond 100 µmol/L, there is a paucity of data in the literature regarding the risk of stillbirths in relation to the severity of the IHCP. The IHCP presentation and complications may vary depending on the serum levels of bile acids and studies have proven that the mild form of IHCP (bile acid levels < 40 µmol/L) is found in higher proportion than the severe form (bile acid levels >40 µmol/L).[11,12] In view of the retrospective nature of the study, we could not stratify the severity of the IHCP based on serum bile acid level and hence the distribution of mild and severe forms of IHCP in women with stillbirths and livebirths remains undetermined in our study. We assume that higher serum bile levels exert more severe effects through vasoconstriction of placental chorionic vessels leading to acute anoxia and sudden fetal death.[13]

A total of 4 cases of AFLP was diagnosed by Swansea criterion during 3 years amounting the incidence to 1 in 18,819 pregnancies which is in tune with that reported in literature ranging from 1: 7,000 to 1:20,000.[14] There is a high incidence of loss of maternal life when inflicted with the condition.[15] The diagnosis in all cases was made after the exclusion of all other morbidities. The vague clinical presentation and non-specific laboratory findings posed a diagnostic dilemma for the clinicians, the reason that the fetal outcome was poor in three cases and maternal outcome in two cases. Yan Zhong et al.[16] reported a much higher incidence in their retrospective study of 6 years (0.14%) in contrast to ours (0.005%).

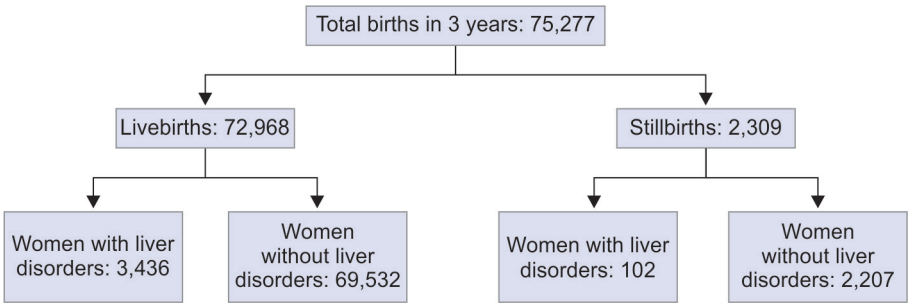

Fig. 1: Flowchart for selection of cases in the study

Table 1: Univariate analysis of the demographic and obstetric characteristics of women with hepatic disorders in pregnancy with stillbirths compared to livebirths

Parameters	*Stillbirths with liver disorders (102), N (%)*	*Livebirths with liver disorders (n = 3,436), N (%)*	*p-value*	*OR (95% CI)*
Mean age ± SD	26.36 ± 4.62	25.86 ± 4.58	0.279	–
Booking status				
Booked	20 (19.60)	1,154 (33.58)	0.033	2.08 (1.02–4.23)
Unbooked	69 (67.64)	1,924 (56)		1.00 (0.55–1.84)
Registered	13 (12.74)	358 (10.41)		1
Residence				
Urban	28 (27.45)	1,182 (34.40)	0.345	–
Rural	63 (61.76)	1,922 (55.93)		–
Slum	11 (10.78)	332 (9.70)		–
Gravidity				
Primigravida	44 (43.1)	1,575 (45.8)	0.589	–
Multigravida	58 (56.9)	1,861 (54.2)		–
Number of ANC visits				
<3 ANC visits or none	83 (81.4)	2,206 (64.2)	<0.05	2.43 (1.47–4.03)
≥3 ANC visits	19 (18.6)	1,230 (35.8)		
Symptoms				
Itching	50 (49)	1,636 (47.6)	0.779	–
Pain abdomen	10 (98)	486 (14.1)	0.213	–
Vomiting	12 (11.8)	359 (10.4)	0.669	–
LOFM	100 (98)	455 (13.2)	<0.05	333 (83–1000)
Average duration of LOFM	1.10 ± 0.389	0.80 ± 0.422	<0.05	
Associated comorbidity				
Abruption	12 (11.8)	57 (1.7)	<0.05	7.9 (4.09–15.24)
Anemia	46 (45.1)	1,604 (46.7)	0.752	–
HTN	13 (12.7)	240 (7)	0.026	1.94 (1.07–3.53)
GDM	9 (8.8)	448 (13)	0.211	–
Hypothyroidism	13 (12.7)	447 (13)	0.938	–
Obstetric complication				
PROM	6 (5.88)	113 (3.28)	0.159	–
Fetal complications				
Congenital anomaly	4 (3.9)	193 (5.6)	0.462	–
Fetal growth restriction	8 (7.8)	138 (4)	0.058	2.03 (0.97–4.27)
Liver function test				
Serum bilirubin	3.34 ± 2.23	2.79 ± 1.88	0.199	–
SGOT	231 ± 202	153 ± 137	<0.05	–
SGPT	239 ± 189	167 ± 134	0.022	–
Alkaline phosphatase	752 ± 368	672 ± 355	0.234	–
Diagnosis				
IHCP	50 (49.01)	2,199 (63.99)	0.002	0.54 (0.36–0.80)
Jaundice	16 (15.7)	229 (6.7)	<0.05	2.60 (1.50–4.51)
HEV	15 (14.7)	158 (4.6)	<0.05	3.58 (2.02–6.33)
HELLP	13 (12.7)	579 (16.9)	0.274	–
Other viral hepatitis	5 (4.9)	271 (7.9)	0.268	–
AFLP	3 (2.9)	1 (0)	<0.05	100 (10.75–1000)
Baby weight at birth	2,154.67 ± 711	2,437 ± 512	<0.05	

ANC, antenatal checkup; GDM, gestation diabetes mellitus; HTN, hypertension; PROM, premature rupture of membranes; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase

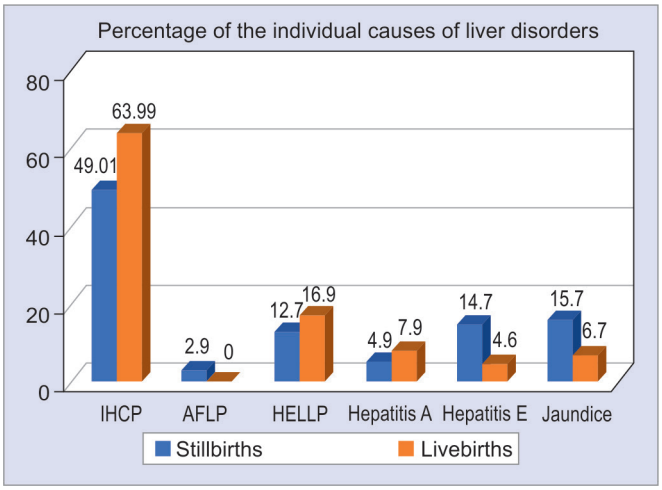

Fig. 2: Hepatic disorders diagnosed in women with stillbirths and livebirths

The authors attributed this fact to their health center being at the highest level in their province thus getting referrals of all severe cases.[16] Acute fatty liver of pregnancy typically presents in the third trimester although there have been reports of AFLP diagnosed in patients as early as 18 weeks and as late as 4 days postpartum.[17,18] All the AFLP cases in our study were diagnosed in the third trimester of pregnancy and were admitted at high-dependency units delivered before term. Two patients delivered spontaneously due to the onset of preterm labor during treatment out of which one baby was livebirth. In the other two patients, induction was done with pharmacological agents immediately after admission since they were diagnosed with stillbirths. Due to the substantial overlap of the signs and symptoms of AFLP and HELLP, the recognition of the entity is often difficult to make thus delaying the diagnosis.

We found that among all cases of viral hepatitis, 38.5% of the cases were caused by HEV. The incidence of stillbirths in HEV-positive women in our study was 8.67%. This is in contrast to findings by Patra S et al. who reported a very high stillbirth rate (54%) among HEV-positive women.[19] Another study by Okwara VC et al. in Nigeria reported only 4.5% stillbirths.[20] There is a wide range of seroprevalence of HEV estimated between 0.6 and 52.5% worldwide with the differences evident even within the same country.[21] The zoonotic nature of the disease with confirmation of three HEV genotypes to infect humans explains the wide variation in its epidemiology.[22,23] We found women with HEV infection had significantly higher odds of delivering stillbirths (OR: 3.58; CI: 2.02–6.33). This is in contrast to a study by Patra S et al. which reported a relative risk (RR = 1.8; CI: 1.2–2.5, $p = 0.026$) lower than ours.[19] The cited study had 33% of women with HEV in the second trimester and 67% in the third trimester while we had all patients in the third trimester. If a woman is infected during the third trimester, there is a high risk of fulminant liver failure along with maternal (up to 30%) and fetal mortality (up to 50%).[24] The pathophysiology of HEV infection in pregnancy has many theories. A possible interaction between the hormonal changes in the form of reduced expression of estrogen and progesterone receptors and immunologic modulations of pregnancy to facilitate a healthy progression of pregnancy may exert undesirable effects in the presence of a high viral load of HEV.[25] This interplay may not significantly increase the risk of adverse pregnancy outcome during early pregnancy but with a gradual decrease in the concentration of the plasma cytokine level in late pregnancy and hence decline in the immune status of the woman, HEV infection may pose a higher risk of adverse fetal outcome in the third trimester.[26]

We found that 12.7% of stillbirths were due to HELLP syndrome. We had a total of 13 stillbirths in a total of 592 cases of HELLP syndrome hence the stillbirth prevalence among the cases of HELLP syndrome was 2.19%. This is almost similar to the study by Lisonkova S et al. who reported a stillbirth rate of 13.5 per thousand cases of HELLP syndrome (1.35%) in their retrospective population-based cohort study in Canada.[27] Furthermore, HELLP is postulated to be the result of the maternal immune response to the physiological changes of pregnancy causing dysfunction of endothelial cells.[28,29] Placental involvement is very often indicated in the pathophysiology of HELLP syndrome evidenced by raised biochemical markers in maternal serum at 15–20 weeks.

There is a mild increase in the levels of aspartate aminotransferase (AST)/alanine transaminase (ALT)/alkaline phosphatase along with a few signs of disseminated intravascular coagulation (DIC) and decreased platelet count in mild preeclampsia. The changes in parameters of coagulation are evident by adhesion of the platelets on the surface of activated and damaged endothelium following which there is release of thromboxane A and serotonin stimulating vasospasm and further platelet aggregation. There is breakdown of red blood cells while passing through these platelet-fibrin-rich capillaries, thus causing microangiopathic hemolytic anemia. Microvascular injury in different organs manifests with a myriad of signs and symptoms. Such damage in the liver causes hepatic necrosis leading to HELLP syndrome.[30] If, however, jaundice is present, it implies hemolysis and a terminal stage of liver disease in HELLP. Levels of fetal messenger RNA for sFlt1 vascular endothelial growth factor receptor-1 (VEGFR-1) and soluble endoglin are found significantly higher in such signaling severe abnormal placentation.[27]

Ngwenya S et al. found that unbooked status [adjusted odds ratio (AOR): 3.01; 95% CI: 2.20–9.10] was found to be a significant contributary factor to the occurrence of stillbirths.[31] We also found the effect of booking status to have a significant effect on the occurrence of stillbirths. Booking visit gives the clinician the chance to detect the disorders disposed to affect the course of pregnancy which is essential to deciding the preventive, curative, and counseling services. The expectant mothers on the other way become aware of the health care services they can avail for themselves.

Clinical Significance

The strengths of our study is the analysis of such a large number of women delivering at a tertiary care institute. To the best of our knowledge, there are hardly any studies which evaluated the incidence of stillbirths in pregnancy with liver disease. The clinical significance of the index article lies in the extensive analysis of different hepatic disorders in pregnancy and its relation to stillbirths.

Limitations

The major limitation of this study is that being a retrospective study, certain antenatal factors predisposing to hepatic infliction could not be elicited.

Conclusion

The incidence of stillbirths due to liver disorders in pregnancy was 4.4%. Hypertension of pregnancy, abruption, fetal growth restriction, and low birth weight were significantly associated with stillbirths. Among all hepatic disorders, jaundice due to medical disorders and HEV were found. significantly high in women with stillbirths.

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Authors' Contributions

- Concept and design: Harsha S Gaikwad; Kashika Nagpal
- Data collection: Poornima; Kashika Nagpal
- Drafting of article: Banashree Nath; Poornima; Harsha S Gaikwad
- Supervision and review of manuscript: Harsha S Gaikwad; Pratima Mittal; Achla Batra

Orcid

Banashree Nath https://orcid.org/0000-0001-5708-8769
Poornima Sharma https://orcid.org/0000-0003-1290-8545
Pratima Mittal https://orcid.org/0000-0002-3268-3681

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