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Original Article

Obstetrics and Gynaecology Section

Risk Factors for Stillbirths: A Case-control Study

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ABSTRACT

Introduction: The occurrence of Stillbirths (SBs) is a tragic event faced by the obstetrician and causes great psychological trauma and emotional devastation to the couple and the family. It is estimated that approximately 3.2 million stillbirths occur in the world every year. The SB rate across India is about 20 per 1,000 live births accounting for highest absolute number of stillbirth in the world.

Aim: To analyse the risk factors for stillbirths in a tertiary teaching centre in northern India.

Materials and Methods: Sample size was calculated to be 150. In the study institution, nearly 600 stillbirths occur annually and since the required sample size was 150, every 4th woman delivering a stillbirth was included as case and the live birth matched for gestational age consecutive to the case was taken as control. All babies of the study and control group were examined by the neonatologist. Mothers of all babies were interviewed through a stillbirth review proforma (by WHO apps SEARO) within 24 hours of delivery. Qualitative data analysis was done by chi-square test and quantitative data by using t-test. The p-value <0.05 was be considered significant. Logistic regression was applied to get odds ratio for the risk prevalence. Variables with statistically significant association on univariate analysis were included in a multivariable binary logistic regression model.

Results: Stillbirth rate was 25.4 per 1000 births. A significant association of pre-existing hypertension (p=0.008) and anaemia (p=0.05) as maternal comorbid conditions were found with stillbirths. There were 66 Fresh SBs (44%) and 84 Macerated SBs (56%). When intrapartum risk factors were analysed, significant association was found with antepartum haemorrhage, cord prolapse, malpresentation, obstructed labour and rupture uterus as compared to control group. On multivariate analysis of various risk factors, maternal age >30 years, maternal BMI >25 kg/m^2, antenatal checkups <3 in number, maternal illiteracy, lack of periconceptional folic acid intake along with pre-existing hypertension, fetal malpresentation, and antepartum haemorrhage were observed to have an independent, significant association with the occurrence of stillbirths.

Conclusion: Among sociodemographic factors, older mothers, obesity, inadequate antenatal checkups, lack of maternal education, lack of periconceptional folic acid intake were associated with high risk of SBs. Maternal morbidity especially pre-existing hypertension which led to antepartum haemorrhage along with fetal malpresentation was observed to have an independent, significant association with the occurrence of SBs. Hence apart from improved intrapartum care, essential screening during antenatal visits with allotment of cards of varied identity with appropriate precedence can be an important step in monitoring the high-risk cases which can also prove crucial in timely referral to tertiary care units.

Keywords: Causal factors, Intrauterine fetal deaths, Prevention

INTRODUCTION

The occurrence of SBs is a tragic event faced by the obstetrician and causes great psychological trauma and emotional devastation to the couple and the family. It is estimated that approximately 3.2 million stillbirths occur in the world every year [1]. Nearly, 66% (1.8 million) of these occur in just 10 countries and India is amongst them with stillbirths ranging from 20-66 per 1000 live births in different states [2,3]. However, despite the large global burden, stillbirths are not highlighted in national and global policies.

According to WHO, for international comparison "Stillbirth" refers to a fetal death late in pregnancy after >28 weeks [4]. The rationale for restricting stillbirths greater than 1000 gm or after 28 weeks for international reporting purposes is to assure comparability because the countries where most of these stillbirths occur still do not capture these deaths and data remains uncertain [5]. Various socio-demographic, maternal and fetal risk factors have been reportedly associated with the occurrence of stillbirths [3]. Amongst all the risk factors reported, some of these were found to be potentially modifiable. Vidyadhar BB et al., observed that a large number of stillbirths are preventable by regular antenatal checkups and institutional delivery [1]. A study from UK reported that most stillbirths are avoidable and that unrecognised Fetal Growth Restriction (FGR), maternal obesity and smoking are potentially modifiable risk factors [6]. The risk factors for antepartum and intrapartum stillbirths differ. Maternal co-morbidities like hypertension, cardiovascular disease, Antepartum Haemorrhage (APH) and fetal factors like FGR, hydrops and congenital Birth Defects (BD) are amongst the significant causes of antepartum stillbirths, while preterm labour, infection and hypoxia are dominant risk factors of intrapartum stillbirths [5]. However, a significant proportion of stillbirths are often categorised as unclassified or unexplained, and these are often considered unavoidable [7].

The present study was designed to study the risk factors associated with stillbirths, (as defined by WHO) [4], in a tertiary care hospital in northern India.

MATERIALS AND METHODS

The present case-control study was conducted in the Department of Obstetrics and Gynaecology for a period of one year, from April 2016 to March 2017, at a tertiary teaching hospital of Northern India, New Delhi, in collaboration with the Department of Community Medicine. In this study, the present authors used the CODAC system of classification of SB causation, as included

in WHO stillbirth proforma. Written and informed consent was taken from all the enrolled women in a language well understood by them. Patients were convinced that the procured information shall be kept confidential and used for academic purposes only. Approval from Institutional Ethical Committee (S.NO.IEC/VMMC/SJH/Thesis/October-2015; Dated 2/11/2015) was obtained before starting the study.

Study Population

All mothers who delivered in the study setting within the study period, either vaginally or by caesarean section were eligible to participate. The sample size was calculated by using the software EpiInfo version 7.0. In a study conducted in Nablus [8], the lowest OR (3.9) among all the clinic-social factors was prematurity. An amount of 6.5% of live births and 48.8% of the stillbirths were born prematurely. Taking this OR and prevalence of prematurity among cases and controls with 95% confidence intervals, 90% power and 10% response error, the minimum calculated sample size came out to be 138 which was rounded off to 150. Hence, 150 cases and 150 controls were taken for the current study.

The enrolled women were divided into two groups as follows:

Cases (n=150): In the study institution, nearly 600 stillbirths occur annually and since the required sample size was 150, every 4th woman delivering a stillbirth was included as case.

Controls (n=150): This comprised of women who delivered a live birth matched for gestational age consecutive to the case.

All babies of the study and control group were examined by the neonatologist for gestational age, signs of maceration and any visible birth defects. Birth weight of newborns was recorded and divided into three groups according to international fetal growth and sex-specific standard [9]. Those newborns having birth weights below the 10th percentile for gestational age were termed as Small for Gestational Age (SGA), those having birth weights between the 10th and 90th percentiles (inclusive) for gestational age were identified as Appropriate for Gestational Age (AGA) while the newborns having birth weights above the 90th percentile for gestational age were defined as Large for Gestational Age (LGA).

Mothers of all babies were interviewed through stillbirth review proforma (by WHO apps SEARO) within 24 hours of delivery. This questionnaire included all details of mothers and babies. Demographic profile of mother was noted. Details regarding any history of consanguinity of marriage, passive or active smoking, history of substance abuse were enquired. Obstetric and medical history was inquired. The details of ingestion of folic acid, peri-conceptionally in present pregnancy, any febrile illness with or without rash and in first trimester, any history of exposure to radiation/drugs. Presence of any antenatal complications including hypertensive disorders of pregnancy, Gestational Diabetes Mellitus (GDM), Intrahepatic Cholestasis of Pregnancy (IHCP), antepartum haemorrhage, anaemia, heart disease was enquired. Any obstetric complication like fetal growth restriction, oligohydramnios or polyhydramnios were enquired for and if possible elicited from medical records and documents.

Gestational age was determined from the date of last menstrual period and confirmation of gestational age was done from earliest USG scan if not sure of dates. Diagnosis at admission and delivery details was noted.

STATISTICAL ANALYSIS

Simple descriptive tabulation was made from the data and analysed by SPSS version 17.0. Qualitative data analysis was done by chi-square test and quantitative data by using t-test. The p-value <0.05 was be considered significant. Logistic regression was applied to get odds ratio for the risk prevalence. Variables with statistically significant association on univariate analysis were included in a multivariable binary logistic regression model. The present authors used logistic regression analysis to examine the adjusted effects of various risk factors on stillbirth. Results are reported as Adjusted Odds Ratios (AORs) and 95% confidence intervals (95% CIs). Independent variables are a number of sociodemographic, maternal and fetal risk factors.

RESULTS

During the study period, there were 27,259 deliveries, out of which 26,566 were live births and 693 were stillbirths, the stillbirth rate being 25.4 per 1000 births. Basic demographic data is presented in [Table/Fig-1]. A significant association with hypertension (p=0.008) and anaemia (p=0.05) as maternal comorbid conditions were found with stillbirths in study group. Other comorbid conditions viz., diabetes mellitus (gestational and overt DM), hypothyroidism, jaundice, HIV infection had no statistically significant difference between the study and control groups. There were 66 Fresh SBs (44%) and 84 Macerated SBs (56%) in the present study. When intrapartum risk factors were analysed, significant association was found with antepartum haemorrhage, cord prolapse, malpresentation, obstructed labour and rupture uterus as compared to control group [Table/Fig-2].

Parameters	Study group (150)	Control group (150)	p-value
Mean maternal age (years)	26.02±5.21	24.54±4.16	0.003
Mean gestational age of delivery (weeks)	35.64±4.3	36.04±1.9	0.765
BMI (>25)	104 (69.34%)	71(47.34%)	0.00003
Unbooked (<3 antenatal check-up)	127 (84.66%)	52 (34.66%)	<0.05
Maternal low SES	101 (67.33%)	54 (36.99%)	<0.05
Maternal illiteracy	49 (32.66%)	23 (15.33%)	<0.05
H/o Consanguinity	3 (2.00%)	2 (1.33%)	1.00*
Resident from rural areas	87 (58%)	48 (32%	<0.05
Parity (≥3)	47 (31.33%)	38 (25.33%)	0.304
Mode of delivery			
Vaginal	126 (84.00%)	126 (84.00%)	1.00
Caesarean	24 (16.00%)	24 (16.00%)	
Male baby	97 (64.66%)	79 (52.66%)	0.035
Size of baby A/t gestational age			
SGA	27 (18.00%)	14 (9.33%)	0.003
AGA	115 (76.66%)	135 (90.00%)	
LGA	08 (5.33%)	01 (0.66%)	

[Table/Fig-1]: Basic demographic and obstetric data.
*p-value: 1.00 (Fisher's Exact Test)

Intrapartum complications	Group		Odds ratio	95% CI	p-value
	Study	Control			
APH	23 (15.33%)	01 (0.66%)	27.0	3.8-544.3	<0.05**
Cord prolapse	17 (11.33%)	0	-	-	<0.05**
Mal presentation	24 (16.00%)	02 (1.33%)	14.1	3.1-88.1	<0.05**
Rupture uterus/ Obstructed labor	07 (4.66%)	0	-	-	0.015**
Chorioamnionitis	03 (2.00%)	0	-	-	0.25**
PPROM/PROM	08 (5.33%)	17 (11.33%)	0.4	0.2-1.1	0.06*
MSL	03 (2.00%)	13 (8.66%)	0.2	0.05-0.8	0.02**
Fetal distress	23 (15.33%)	15 (10.00%)	1.6	0.8-3.5	0.16*
Preterm labor pains	04 (2.66%)	08 (5.33%)	0.5	0.1-1.8	0.38

[Table/Fig-2]: Distribution of intrapartum complications in study group and control group.
*Chi-square test; **Fisher-Exact test
APH: Antepartum haemorrhage; PPROM/PROM: Preterm premature rupture of membranes/ Premature rupture of membranes; MSL: Meconium stained liquor

The present study observed (CODAC classification, [Table/Fig-3]) that the highest proportion of stillbirths was attributable to maternal causes and maternal associated conditions. The proportion of unexplained SBs in the present study was 18%. On multivariate analysis of various risk factors [Table/Fig-4], maternal age >30 years, BMI >25 kg/m^2, antenatal checkups <3 in number, maternal illiteracy, lack of periconceptional folic acid intake along with pre-existing hypertension, fetal malpresentation, and antepartum haemorrhage were observed to have an independent, significant association with the occurrence of stillbirths. No significant association was observed between history of passive smoking, fever with rash, previous stillbirths, consanguinity of marriage, previous birth defects, parity or mode of delivery with occurrence of stillbirths.

CODAC*	n	Percentage
Infections	02	1.33%
Intrapartum complications	42	28.00%
Placental causes	30	20.00%
Cord complications (Cord prolapse)	16	10.66%
Maternal causes (Hypertension)	51	34.00%
Maternal Asso. Conds (Anaemia, passive smoking)	74	49.33%
Fetal causes	16	10.66%
Fetal Asso. Conds (FGR)	33	22.00%
Unknown	27	18.00%

[Table/Fig-3]: Cause of stillbirths according to CODAC classification.

Parameters	Odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Maternal age >30 years	2.68 (1.62-4.42)	<0.05	1.067 (1.00-1.13)	0.03
Gestational age at delivery ≤34 weeks.	9.03 (3.92-20.81)	<0.05	7.446 (3.31-15.63)	<0.05
BMI of mother (kg/m^2) >25	2.51 (1.56-4.03)	<0.05	2.53 (1.37-4.67)	<0.05
Unbooked (<3 antenatal check-up)	10.40 (5.9-18.16)	<0.05	9.389 (5.09-17.31)	<0.05
Maternal low SES	3.66 (2.27-5.90)	<0.05	0.883(0.32-2.36)	0.80
Maternal illiteracy	2.67 (1.53-4.69)	<0.05	3.72 (2.06-6.74)	<0.05
H/o Passive smoking in mother	1.56 (0.86-2.85)	0.12	-	-
No H/o Periconceptional folic acid intake by mother.	2.84 (1.77-4.55)	<0.05	1.94 (1.05-3.70)	0.03
Fever with rash	2.0 (0.3-16.2)	0.68	-	-
H/o Prev. SB	2.6 (0.4-19.3)	0.45	-	-
H/o Consanguinity	1.5 (0.2-13.1)	1.00	-	-
Gross congenital anomaly in baby	2.47 (0.92-6.61)	0.06	-	-
Parity (≥3)	1.30 (0.78-2.16)	0.304	-	-
Male baby	1.6 (1.0-2.7)	0.035	0.74 (0.44-1.2)	0.23
Mode of delivery				
Vaginal/caesarean	1.0 (0.52-1.94)	1.00	-	-
Diabetes	0.66 (0.362-1.20)	0.17	-	-
Weight of baby <2.5 kg	1.31 (0.83-2.08)	0.24	-	-
Malpresentation Yes	14.1 (3.26-60.81)	<0.05	13.70 (2.93-64.04)	<0.05
HTN Yes	2.1 (1.2-3.9)	0.008	2.691(1.362-1.362)	0.004
APH Yes	28.4 (4.01-571.6)	<0.05	19.09 (2.51-145.16)	0.004

[Table/Fig-4]: Univariate and Multivariate analysis of multiple risk factors associated with stillbirths.

DISCUSSION

Stillbarth Rates (SBRs)

The study observed an overall SBR of 25.4 per 1000 births. It has been reported that globally, almost 98% of SBs occur in Low and Middle-income Countries (LMICs) with low resource settings with an estimated SBR of 25.5 per 1000 deliveries while the same in the developed world is reported to be just 3.4 per 1000 deliveries [10]. The different SBRs in developing and developed nations reflect the quality of antenatal and intra-natal obstetric care delivered to women in these economically developed nations as compared to developing countries [10].

Socio-Demographic Risk Factors

The present authors observed a significant association of lower socioeconomic status and maternal illiteracy with the occurrence with SBs like many other studies [1,6]. Lower maternal education is associated with lower socioeconomic status and the two factors together lead to ignorance about the significance of antenatal supervision and the concept of high-risk pregnancy, thus increasing the risk of SB which was well reflected in the index study. A significant association with failure to take periconceptional folic acid and occurrence of SB was discovered in the present study which was established already by some observational studies [11-13]. Folate deficiency may increase the risk of stillbirths through vascular effects causing higher incidence of abruptio placentae and pre-eclampsia [14], the significantly higher incidence of which was evident in the present study too. Patients with irregular antenatal checkups were at higher risk of stillbirth. Ashish KC et al., reported that the risk of having an antepartum SB was 4.5 times higher compared to those who attended at least one antenatal care visit [15]. Lawn JE et al., reported that national SBRs have a strong association with the coverage of antenatal care [10]. In the present study women with less than three antenatal visits had higher incidence of fetal growth restriction and abruption due to loss of opportunity to screen mothers and diagnose complications early. There was failure to provide counselling for healthy pregnancy as well. The present study observed most of the women delivering stillbirths belonged to rural areas. Other Indian studies [1,16] reported similar findings. A study from Nepal [17] (aOR, 1.31; 95% CI, 1.00 to 1.72) and Bangladesh [18] (OR1.36; 95% CI, 1.13 to 1.65) also reported higher chance of stillbirth in women who lived in rural areas than in urban areas. Lawn JE et al., in their SB series had highlighted that worldwide also, about 60% of SBs are reported from rural areas due to restricted access to antenatal care, emergency obstetric care like caesarean sections, family planning services and scarcity of transport to nearby health facilities [10].

Maternal Risk Factors

Maternal age has been reported as an important independent risk factor for stillbirths [7,10]. With significant increase in mean age of mothers in study group, the index study reinforces the finding. This may be partially explained by increased incidence of obesity (BMI >25), anaemia and hypertension in the study group. The present study found that women who were overweight (BMI >24.9) had a higher risk of having a SB than women who had a normal BMI like other studies [7,10]. Amark H et al., reported in a register-based cohort study, that the prevalence of stillbirth was higher in pregnancies complicated by overweight/obesity (>25 kg/m^2) than in women with normal BMI (BMI 18.5-24.9 kg/m^2) [19]. The mechanism is explained by the positive correlation of maternal obesity with hypertensive disorders, antepartum haemorrhage and gestational diabetes which is also risk factors of SBs. Hypertension was found significantly high in study group.

The present observations are in concurrence with other studies [1,2]. A systematic review by Flenady V et al., highlighted a strong association between APH, especially placental abruption and SBs [7]. The cause of stillbirths in hypertensive pregnancies is probably due to placental dysfunction and many of them could be averted by timely detection, appropriate management in antenatal care and improved intrapartum care [10]. However, gestational diabetes and over diabetes were found in higher number without statistical significance in the present study. The entire study population belonged to low and middle socioeconomic status who earned livelihood with various means of daily labour work either indoor or outdoor. This could probably explain the low incidence of this metabolic disorder in the population. The present study observed no association of stillbirths with parity of mother like others [2,20]. However, Aliyu et al., observed that the risk for stillbirth increased consistently with increasing parity when moderate parity (1-4) was assumed as reference category after adjusting for potential confounders [21]. The present authors assume small sample size along with relatively younger mothers in the present study failed to establish any existing linkage between parity and stillbirth, if one exists. Intrapartum complications viz., cord prolapse, malpresentation and obstructed labour/rupture uterus were having significant association with SBs. In 2015, globally, out of 2.6 million third trimester stillbirths, an estimated 1.3 million were intrapartum SBs; the proportion varies from 10.0% in developed regions, to 59.3% in south Asia. Intrapartum SB or FSB is a sensitive marker of SBs which are preventable through improved care during labour [10].

Fetal Factors

A higher proportion of stillbirths were SGA and LGA as compared to live births. This was consistent with Contag S et al., who observed that risk of stillbirth increases when birthweight is below the 5th and above the 95th centile which was most evident after 37 weeks [22]. Zhang X et al., observed birth weights of babies born preterm were abnormal, but preterm stillbirths were more growth-restricted than preterm live birth. This study suggested that in-utero restriction of fetal growth is a cumulative process and the fetuses dying subsequently grow slower than those live births born at the same gestational age. Decrease in placental blood supply causing reduced supply of oxygen and nutrients to developing fetuses may result in restriction of growth of fetus in early gestation and subsequently increase the risk of stillbirth [23]. The present authors observed that male sex was significantly associated with the risk of a SBs (p=0.03) in univariate analysis but none with multivariate analysis. Lawn JE et al., reported that male babies are at a 10% higher risk of SB [10]. There are differences in the development of male and female gender which starts very early in life. Male fetuses have faster development and higher metabolic rates than females [24,25], as evidenced in animal models hence exposing the male fetus to a variety of stressors which may include oxidative stress, changes in endocrine function, and nutritional compromise. The present study reported high rate (9.33%) of congenital anomalies among stillbirths as diagnosed by examination by neonatologist at birth out of which neural tube defects scored the highest. A recent meta-analysis also showed central nervous system defects were found in highest among stillbirths which calls for conduction of folic acid supplementation programme in the preconception period, with the need for nation-wide studies on its implementation [26].

LIMITATION

The present study was a purely hospital-based study; therefore it lacks the data of stillbirths occurring in the community. Histo-pathological examination of the placenta and autopsy of SBs were not done which could have shed light on causes of death of SBs classified as unexplained SBs.

CONCLUSION

Maternal age >30 years, BMI >25 kg/m^2, antenatal checkups <3 in number, maternal illiteracy, lack of periconceptional folic acid intake along with pre-existing hypertension, fetal malpresentation, and antepartum haemorrhage were observed to have an independent, significant association with the occurrence of stillbirths. Apart from improved intrapartum care, essential screening during antenatal visits with allotment of cards of varied identity with appropriate precedence can be an important step in monitoring the high-risk cases which can also prove crucial in timely referral to tertiary care units.

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