

Factors Associated with Adverse Neonatal Outcome in Singleton Pregnancy: A Hospital Based Case-Control Study

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Abstract:

Background: One of the sustainable development goals for 2030 is to reduce infant mortality. Unfavourable birth outcomes are the main cause of infant morbidity and mortality. This study looked into the factors associated with adverse foetal outcomes in Bangladesh.

Methods: The case-control study was conducted in BIRDEM general Hospital over 210 singleton pregnant women following 1975 Helsinki declaration and its later amendment. Cases (n=105) were considered as having any adverse birth outcome, while controls (n=105) had none of the adverse birth events. Data were recorded in separated case-record form and analyzed by SPSS-24.

Results: Mean age of cases and controls were 28.98±5.48 (SD) years and 28.65±4.65 years, respectively (p=0.635). Preterm labour (64.8%), low birth weight (LBW, 41.9%) and neonatal intensive care unit (NICU) admission (31.4%) were the common adverse outcomes. Cases had significantly higher prevalence of obesity (24.8% vs 13.3%, p=0.035), gestational diabetes mellitus (49.5% vs 33.3%, p=0.017), pregnancy-induced hypertension (PIH, 40% vs 17.1%, p<0.001) and premature rupture of membrane (PROM, 15.2% vs 4.8%, p=0.011). Maternal age >35 years (adjusted odds ratio=3.77, 95%CI=1.12-12.65), PIH (AOR=3.602, 95%CI=1.797-7.22), and PROM (AOR=5.74, 95%CI=1.83-18.00) were the significant risk factors for adverse foetal outcome. Besides, PIH had significant odds ratio for preterm labour (AOR=2.21, 95%CI=1.13-4.33), LBW (AOR=4.19, 95%CI=1.93-9.12) and NICU (AOR=8.93, 95%CI=3.73-21.38). Maternal age >35 years (AOR=3.21, 95%CI=1.04-9.88) and PROM (OR=3.65, 95%CI=1.18-11.3) were associated with LBW, while previous caesarian section (CS) was responsible for preterm labour (AOR=2.298, 95%CI=1.09-4.87).

Conclusion: Pregnancy with advance maternal age, PIH, previous CS and PROM were the determinants of adverse birth outcomes.

Keywords: Adverse birth outcome, Preterm labour, Low birth weight, Pregnancy induced hypertension

Background:

One of the major Sustainable Development Goals needed to achieve at 2030 is reduction of neonatal death and improvement of their health, even then neonatal mortality is still unacceptably high. Globally, perinatal mortality (stillbirth and early neonatal mortality) accounts for >5 million deaths every year.¹ Adverse birth outcomes especially LBW and preterm

births are at greater risk for mortality, morbidity and several short and long-term physical, developmental and psychological problems. Adverse pregnancy outcome also leads to significant direct and indirect emotional and economic effects on the infant's family and the societies. Hence, unfavorable pregnancy outcomes are the most crucial statistics that are used to assess mother and child health programs and develop evidence-based interventions.

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Maternal and neonatal morbidity and mortality is still a challenging problem in developing and resource limited countries, like Bangladesh. Under-5 mortality in the 5 years preceding the 2017 BDHS is 45 deaths per 1,000 live births. The infant mortality rate is 38 deaths per 1,000 live births, and the child mortality rate is 7 deaths per 1,000 children. The neonatal mortality rate is 30 deaths per 1,000 live births; which accounts for 67% of all under-5 deaths.²

Adverse pregnancy outcomes are influenced by a myriad of biological, social and environmental factors. Biological factors like advanced maternal age, gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH), obesity, previous caesarian section and several antenatal complications- urinary tract infection (UTI), premature rupture of membrane (PROM), oligohydramnios, etc. have been found to be associated with adverse pregnancy outcome.³ Moreover, various epidemiological studies have also suggested association of adverse birth outcome with maternal education level, low socio-economic status, environmental exposures such as environmental tobacco smoke, air pollution and chemicals.⁴ However, there is still very limited data in our country context regarding factors responsible for perinatal morbidity and mortality, which hinders the policy makers and program implementers to pass evidence based informed decisions and to achieve target neonatal outcomes.

Bangladesh has implemented different strategies to decrease fetal, neonatal, and infant mortality. A few of these strategies included improving ante-natal care follow-up, strengthening institutional delivery, early detection and treatment of problems and pre-existing disorders throughout pregnancy. However, due to weak prevention initiatives and a lack of knowledge about the determinants of unfavorable pregnancy outcomes, the adverse pregnancy outcome is still substantially more common in Bangladesh. Therefore, this study was aimed to identify predictors of adverse pregnancy outcome among mothers who gave birth at a tertiary hospital of Bangladesh. The findings of this study may help decision/policymakers as well as clinicians at different levels for designing empirical and evidence-based prevention strategies for adverse pregnancy outcomes.

Methodology:

This case-control study was performed in the Obstetrics and Gynaecology department, BIRDEM General Hospital, from January 2016-December 2017.

A total of 210 singleton pregnant women who gave birth at/after 28 weeks of gestation were included in this study. Cases (n=105) were considered as having any adverse perinatal event, while control (n=105) mothers didn't experience none of the adverse perinatal events. At first, mother was selected using simple random sampling technique among mothers who gave birth on the first day of data collection (then, after the first mother selected, the next was continued based on their discharge from postpartum ward). Finally, systematic random sampling technique was employed to select the final study participants till the required sample size for case and controls were saturated.

Data collection tool and procedure: First the questionnaire and checklist were prepared after reviewing different related articles and documents. The questionnaire was reviewed by senior researchers and pre-tested in randomly selected 5 cases and 15 controls before actual data collection, and some minor modifications were made accordingly. The questionnaire contained a total of three major parts (mother's sociodemographic data, obstetric related data and neonatal outcomes). All pregnant women who gave birth at study center during study period were interviewed and their chart was reviewed after admitted to labor and delivery ward. All methods were performed in accordance with the relevant guidelines and regulations. The principal investigators throughout the data collection process were in close contact and under close supervision. Data from the cases and controls were obtained in a similar approach, reducing information bias.

Operational definitions:

Adverse perinatal outcome (unfavorable): the occurrence of at least one of the following: low birth weight, preterm birth, low Apgar score (<7) at first or fifth minutes after birth, still birth, gross congenital anomaly or neonatal death within 24 hours.

Preterm labour was defined as delivery before 37 weeks of gestation.

Low birth weight (LBW) was defined as a live newborn weighing less than 2,500 g, irrespective of the period of gestation. Macrosomia was considered as baby weighed >4000 gm. All babies were weighed immediately after birth.

Neonatal jaundice was defined as elevated total serum bilirubin (>5 mg/dL) and clinically manifests as

yellowish discoloration of the skin, sclera, and mucous membrane.

Foetal growth restriction was defined as less than 10 percent of predicted fetal weight for gestational age. *Foetus showing signs of inadequate oxygenation was considered as foetal distress.*

Congenital anomaly was when the newborn had been diagnosed with gross congenital anomaly (hydrocephalus, spinal bifida, microcephaly, anencephaly, cleft lip or pallet and polydactyl).

Pregnancy induced hypertension (PIH) was defined as systolic blood pressure \geq 140 mmHg and/or diastolic blood pressure \geq 90 mmHg with one of four conditions: a) pre-existing hypertension, b) gestational hypertension and preeclampsia, c) pre-existing hypertension plus superimposed gestational hypertension with proteinuria, and d) unclassifiable hypertension.

Gestational diabetes mellitus (GDM) was defined as FBG < 7.0 mmol/L at the time of the first pregnancy check-up and meets the requirements of FBG \geq 5.1 mmol/l, 1-hour PBG \geq 10.0 mol/l or 2-hour PBG \geq 8.5 mmol/l during the 75 g glucose tolerance test in 24 - 28 weeks of pregnancy.

Premature rupture of membranes (PROM) was defined as the rupture of the fetal membranes before the onset of labor.

Polyhydramnios was diagnosed when a mother's amniotic fluid index elevates to $>24 \pm 2$ cm standard deviation (SD) in the late second or third trimester. Amniotic fluid index <5cm was considered as oligohydramnios.

Ethical statement: The study was approved by the Ethics Committee of the BIRDEM general Hospital. Informed written consent was taken from each mother or legally authorized representative (for women who cannot read and write/illiterate). Confidentiality of the information was secured throughout the study process.

Data acquisition and statistical analysis: All the data were entered into the SPSS package (version 24). Continuous data were expressed as mean and standard deviation and categorical data were expressed as frequency and percentage and comparisons were assessed by student t-test and chi-square test for continuous and categorical variables respectively. Univariate and multiple logistic regression were done to detect odds ratio (OR) of maternal risk factors. All explanatory variables in univariate logistic regression with p-value <0.05 were considered for multivariate logistic regression analysis to control

confounding factors. Adjusted Odds Ratio (AOR) with their corresponding 95% confidence intervals (CI) was used to declare the independent predictor of adverse birth outcome. A probability (p) value of <0.05 were considered statistically significant.

Result:

Mean age of cases and controls were 28.98 ± 5.48 (SD) years and 28.65 ± 4.65 (SD) years, respectively ($p=0.635$). Maternal age >35 years was more in cases than controls (14.3% vs 3.8%, $p=0.008$). Gestational age at delivery was significantly higher in controls compared to cases (37.49 ± 0.80 vs 35.51 ± 2.17 weeks, $p<0.001$). Cases had significantly higher prevalence of having obesity (24.8% vs 13.3%, $p=0.035$), gestational diabetes mellitus (49.5% vs 33.3%, $p=0.017$), gestational hypertension (40% vs 17.1%, $p<0.001$), uncontrolled hyperglycaemia (31.4% vs 14.3%, $p=0.003$) and premature rupture of membrane (15.2% vs 4.8%, $p=0.011$). However, both groups were statistically similar regarding parity, hypothyroidism, anaemia, previous history caesarian section, antenatal urinary tract infection, polyhydramnios, oligohydramnios and post-partum haemorrhage ($p>0.05$). [Table 1]

Among cases, preterm labour (64.8%) was the most common adverse outcome. Other unfavourable events were low birth weight (41.9%), macrosomia (5.7%), neonatal jaundice (8.6%), intra-uterine growth retardation (9.5%), foetal distress (4.8%), microcephaly (7.6%), anencephaly (1%), and other congenital anomalies (1.9%). Overall, thirty-three neonates (31.4%) of cases needed intensive care. [Figure 1]

Multivariate logistic regression analysis found that maternal age >35 years (OR=3.77, 95% CI= 1.12-12.65), PIH (OR=3.602, 95%CI= 1.797-7.22), and PROM (OR=5.74, 95%CI= 1.83-18.00) were the significant risk factors for adverse foetal outcome. [Table-2]

Table-3 showed that PIH had significant odds ratio for preterm labour (OR=2.21, 95%CI= 1.13-4.33), LBW (OR=4.19, 95%CI= 1.93-9.12) and NICU admission (OR=8.93, 95%CI=3.73-21.38) after adjusting other risk factors- age, obesity, GDM, HbA1C, PROM and previous CS. Besides, maternal age > 35 years (AOR=3.21, 95%CI= 1.04-9.88) and PROM (OR=3.65, 95%CI= 1.18-11.3) were associated with delivering LBW babies. Moreover, previous history of CS was the significant risk factor for preterm labour (AOR= 2.298, 95%CI= 1.09-4.87). [Table-3]

Table-I
Demographic profile of cases and controls (n=210)

Variables	Control (n=105)	Case (n=105)	p-value
Maternal age at delivery (years)			
≤35	101 (96.2)	90 (85.7)	0.008 ^á
>35	4 (3.8)	15 (14.3)	
Mean±SD	28.65±4.65	28.98±5.48	0.635 ^á
Gestational age at delivery (in weeks)	37.49±0.798	35.51±2.17	<0.001 ^á
Maternal height (cm)	153.01±5.64	152.79±5.72	0.78 ^á
Pre-pregnancy maternal height (cm)	63.66±9.24	65.04±9.74	0.296 ^á
Pre-pregnancy maternal BMI (kg/m ²)	27.19±3.69	27.84±3.76	0.205 ^á
Para			0.245 ^á
Primiparous	73 (69.5)	65 (61.9)	
Multiparous	32 (30.5)	40 (38.1)	
Clinical factors			
Obesity	14 (13.3)	26 (24.8)	0.035 ^á
Gestational diabetes mellitus	35 (33.3)	52 (49.5)	0.017 ^á
HbA1C (%)			0.003 ^á
≤6.5	90 (85.7%)	72 (68.6%)	
>6.5	15 (14.3%)	33 (31.4%)	
Pregnancy induced hypertension	18 (17.1)	42 (40.0)	<0.001 ^á
Hypothyroidism	3 (2.9)	4 (3.8)	1.00 ^á
Anaemia	54 (51.4)	64 (61.0)	0.164 ^á
Previous CS	18 (17.1)	24 (22.9)	0.301 ^á
Ante-natal UTI	9 (8.6)	14 (13.3)	0.269 ^á
PROM	5 (4.8)	16 (15.2)	0.011 ^á
Polyhydramnios	5 (4.8)	3 (2.9)	0.337 ^á
Oligohydramnios	7 (6.7)	6 (5.7)	0.775 ^á
PPH	6 (5.7)	10 (9.5)	0.298 ^á

SD=standard deviation, BMI= Body mass index, CS= caesarian section, UTI= Urinary tract infection, PROM= Premature rupture of the uterus, PPH= post-partum haemorrhage

Values are expressed mean±SD and within parenthesis percentage (%) over column in total
p-value was determined by ^áChi-squared Test (c²), ^áIndependent sample T test and ^áFisher's exact test

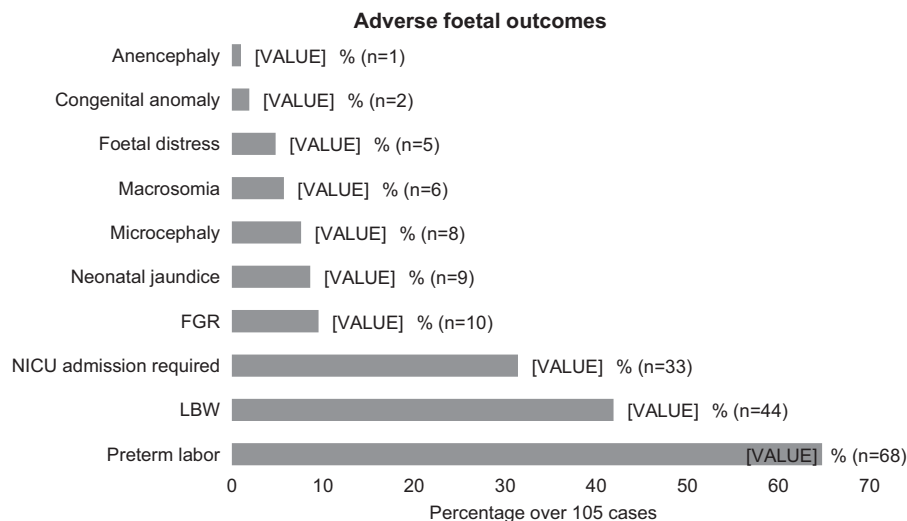


Fig.-1: Adverse foetal events of cases (n=105)

Multiple events considered in a single case

FGR= Foetal growth retardation, LBW= low birth weight, NICU= Neonatal intensive care unit

Table-II
Maternal risk factors for adverse foetal outcomes (n=210)

Predictor	Univariate				Multivariate			
	COR	95% CI		p-value	AOR	95% CI		p-value
		Lower	Upper			Lower	Upper	
Age >35	4.21	1.35	13.15	0.013	3.769	1.123	12.651	0.032
Obesity	2.14	1.05	4.38	0.037	2.068	0.934	4.582	0.073
GDM	1.96	1.12	3.43	<0.001	1.613	0.728	3.573	0.239
Gestational hypertension	3.22	1.70	6.11	<0.001	3.602	1.797	7.221	<0.001
HbA1C >6.5%	2.75	1.39	5.45	0.035	1.782	0.681	4.663	0.239
PROM	3.6	1.27	10.21	0.016	5.732	1.825	18.002	0.003
Previous CS	1.43	0.72	2.83	0.302	1.495	0.695	3.212	0.303

AOR=Adjusted odds ratio, COR= Crude odds ratio, CI=confidence interval CS=Caesarian section, GDM=Gestational diabetes mellitus, PIH=Pregnancy induced hypertension, PROM= Premature rupture of the uterus.

Table-III
Risk factors for preterm delivery, low birth weight baby and NICU admission (n=210)

Predictor	Preterm labour		LBW		NICU admission	
	AOR (95% CI)	p-value	AOR (95% CI)	p-value	AOR (95% CI)	p-value
Age >35 years	1.038 (.36-3.98)	0.945	3.206 (1.04-9.88)	0.043	0.235 (0.05-1.24)	0.088
Obesity	1.835 (0.86-3.93)	0.119	1.607 (0.62-4.19)	0.332	1.071 (0.37-3.09)	0.899
GDM	0.803 (0.34-1.92)	0.623	1.391 (0.50-3.84)	0.524	1.169 (.39-3.53)	0.783
PIH	2.213 (1.13-4.33)	0.020	4.189 (1.93-9.12)	<0.001	8.934 (3.73-21.38)	<0.001
HbA1C >6.5%	2.274 (0.84-6.13)	0.104	1.777 (.55-5.7)	0.333	1.048 (0.28-3.94)	0.945
PROM	2.622 (0.98-6.99)	0.054	3.650 (1.18-11.3)	0.025	2.166 (.62-7.54)	0.225
Previous CS	2.298 (1.09-4.87)	0.030	1.43 (0.3-6.7)	0.14	0.221 (0.05-1.05)	0.057

AOR=Adjusted odds ratio, CI=confidence interval CS=Caesarian section, GDM=Gestational diabetes mellitus, LBW= low birth weight, NICU= neonatal intensive care unit, PIH=Pregnancy induced hypertension, PROM= Premature rupture of the uterus.

Discussion:

Adverse birth outcomes continue to be one of the biggest global public health issues, especially in developing nations like Bangladesh where access to and use of medical services are still relatively low. This study analysed the factors responsible for adverse foetal outcomes in Bangladesh.

This study found that maternal age >35 years had significant odds ratio for adverse birth outcome, especially to deliver LBW babies (AOR=3.21, 95%CI= 1.04-9.88), which is supported by studies conducted in Bangladesh⁵, China⁶, and Ethiopia⁷. A multi-country evaluation encompassing 29 middle- and low-income nations came to the same conclusion that advanced maternal age was a risk factor for LBW (OR= 1.1, 1.4 and 1.2 for women aged 35–39, 40–45 and e" 45 years old, respectively)⁸. The high prevalence of obstetric complications and associated iatrogenic preterm

difficulties in older pregnancies may be the cause of this similarity. Changes in social and economic conditions, as well as improvements in assisted reproductive technologies, have all contributed to delays in childbearing. These factors add to the risk of developing disorders during gestation that are unrelated to pregnancy. Adverse perinatal outcomes are therefore more frequent in older patients. Hence, raising public knowledge of the adverse impacts of late childbearing is necessary.

In current study, cases had significantly higher prevalence of obesity (24.8% vs 13.3%, p=0.035) than controls. Several previous studies also found the similar adverse birth outcome in obese mothers.^{9,10} Although the precise mechanism underlying this relation is yet unknown, the most likely cause may be the close association between maternal obesity and the frequent co-occurrence of diabetes and hypertension in the same

patient. This study also noticed that cases had significantly higher prevalence gestational diabetes mellitus (49.5% vs 33.3%, $p=0.017$), and pregnancy induced hypertension (40% vs 17.1%, $p<0.001$). These findings are also in conformance with the work of previous researchers^{11–13}

In present study, pregnancy induced hypertension had significant odds ratio for adverse birth outcome, especially for preterm delivery (AOR=2.21, 95%CI= 1.13-4.33), LBW (AOR=4.19, 95%CI= 1.93-9.12) and admission to neonatal intensive care unit (AOR=8.93, 95%CI=3.73-21.38). Similarly, an Ethiopian study also noticed that women with pregnancy-induced hypertension were born babies with a higher risk of low birth weight (AOR=5.1, 95%CI=3.4-7.8), preterm labour (AOR=5.2, 95%CI=3.4-7.9), and NICU admission (AOR=5.1, 95%CI=3.1-8.4) compared to normotensive pregnant women after adjusted for confounders.¹⁴ A study from Malaysia found pregnancy-induced hypertension as an independent risk factor (AOR = 5.06; 95%CI= 2.63-9.71) for low birth weight after controlling for important confounders such as maternal age, ethnicity, education, parity, gestational age at delivery, and previous history of abortion.¹⁵ Additionally, biological explanations for the connection between pregnancy-induced hypertension and low birth weight have been put forth due to placental insufficiency. Thus, low birth weight and foetal growth retardation are caused by the reduced utero-placental blood perfusion. Besides, different interventional delivery methods used on eclamptic women regardless of gestational age also may contribute to the high rate of preterm delivery in pregnancy induced hypertension.¹⁴ Alarming, complications from preterm birth and low birth weight are the leading cause of child deaths every year. Current study also found that preterm labour and low birth weight were the most common adverse birth outcomes. Previous studies of Bangladesh^{16,17} also reported prematurity and LBW as the most commonly encountered unfavourable birth events. Hence, to further lower the risk of premature delivery and LBW, an integrated effort from all stakeholders should be maintained and relevant interventions should be developed, especially to control pregnancy induced hypertension.

In this study, premature rupture of membrane (15.2% vs 4.8%, $p=0.011$) was occurred more in cases than controls. Besides, PROM had significant odds ratio

for adverse birth outcome (AOR=5.73, 95%CI= 1.82-18). Similarly, Degno et al., also observed that mothers who had PROM during the current pregnancy were approximately two times more likely to have adverse birth outcome than mothers who had no PROM (AOR = 2.31, 95%CI= 1.26–4.21; $P = 0.006$).¹⁸

This study also found that previous history of CS was the significant risk factor for preterm labour (AOR= 2.298, 95%CI= 1.09-4.87). In a secondary analysis of World Health Organization multi-country survey on maternal and newborn health also reported that previous CS was associated with increased risk of preterm birth (AOR=1.07; 95% CI=1.01-1.14).¹⁹ Besides, according to a prior study conducted in a sizable cohort of pregnant women in the United States, pregnant women with prior CS were 14% more likely to have a preterm birth in their subsequent pregnancy (95% CI= 1.12 to 1.16).²⁰ These findings highlight that efforts to limit unnecessary CS may lead to lowering the preterm birth rate.

Our study has some potential limitations. It was a single centered and small sized study. Besides, we did not investigate the effect of socio-economic, genetic and environmental factors. Moreover, diet history, family violence and psychological status of pregnant mothers were also not evaluated.

Conclusion:

Pregnancy with advance maternal age, gestational diabetes mellitus, pregnancy induced hypertension, previous caesarian section and premature rupture of membrane were found to be associated with adverse birth outcome. Therefore, it is better for health care providers to counsel couples, who seek to have a child in their later ages, about the risks of advanced maternal age, especially in those who had previous history of caesarian section. Necessary steps should be taken to control blood glucose and pressure during pregnancy. Besides, mothers should be encouraged for regular antenatal visit for prevention, early diagnosis and prompt management of premature rupture of membrane.

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