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The association between maternal anemia and preterm birth: A case-control study

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A B S T R A C T

Introduction: Preterm birth (PTB), defined as birth before 37 weeks of gestation, remains a global public health challenge associated with neonatal morbidity and mortality. Maternal anemia, characterized by low hemoglobin levels, is prevalent in many low- and middle-income countries, including Pakistan.

Methodology: A case-control study was conducted at Swat Medical College and Women Hospital Mardan, Pakistan, from June 2022 to June 2023. Medical records of 1000 pregnant women (500 cases of PTB and 500 controls of term births) were reviewed. Maternal anemia, defined as hemoglobin levels below 11 g/dL, was assessed along with demographic variables, pregnancy history, and maternal complications. Logistic regression analysis adjusted for potential confounders was performed to determine the association between maternal anemia and PTB.

Results: Maternal anemia was significantly associated with an increased risk of PTB (adjusted odds ratio [OR] = 2.50; 95% confidence interval [CI]: 1.80-3.50; $p < 0.001$). Other significant risk factors included previous PTB (adjusted OR = 2.20; 95% CI: 1.50-3.20; $p < 0.001$), multiparity (adjusted OR = 1.50; 95% CI: 1.10-2.00; $p = 0.01$), preeclampsia (adjusted OR = 3.00; 95% CI: 2.20-4.20; $p<0.001$), and gestational diabetes (adjusted OR = 2.00; 95% CI: 1.50-2.70; $p<0.001$). Demographic factors such as maternal age, education, residence, and pre-pregnancy BMI did not show significant associations with PTB.

Conclusion: Maternal anemia emerges as a significant risk factor for PTB in Pakistan. Early detection and management of anemia during pregnancy are crucial to reducing the burden of PTB and its associated adverse outcomes.

Keywords: *Preterm Birth, Neonatal Morbidity, Hemoglobin level, Maternal Anemia, Prenatal care, Preeclampsia, Pregnancy outcomes.*

Introduction

Preterm birth (PTB), occurring in the 8th month of pregnancy, is the reason of neonatal mortality and one of the main leading causes of mortality in children under the age of five.[1] PTB rates fluctuate worldwide and have risen slowly in the past few years, from 5% to 18%.[2] With 14.8 million births, the overall PTB rate in 2014 was 10.6%; of those, almost 12 million (81.1%) were in Asia and Sub-Saharan Africa.[3]

PTB is related to a 50% morbidity and death rate.[4] Furthermore, many newborns with PTB have compromised short- and long-term survival outcomes, which may involve behavioral problems, a reduced quality of existence linked to fitness, cognitive impairment, learning abilities, lack of concentration, malnutrition, neurological diseases, and in certain situations, chronic ailments that can prove fatal.[5] PTB has an impact on newborns as well as higher family and healthcare expenses.[6] The prevalence of iron deficiency in pregnancy specially at 3rd trimester in underdeveloped countries like Pakistan was reported to be 22.5% in previous decade but now it's increased up to 52% which is very alarming and required a lot of attention. The

World Health Organization (WHO) has reported 10.3% for anemia in women aged 25 to 39 years of age all over the world during pregnancy.

Previously reported data has demonstrated that iron deficiency anemia during pregnancy relates to PTB,[7-8] while others are unable to substantiate this link.[9-10] This disparity might be attributed to Hb values performed throughout various trimesters,[11-13] or to the failure to adjust for common confounding variables. This study aimed to explore the association between maternal anemia during the first and second trimesters, as determined by average hemoglobin (Hb) levels, and preterm birth (PTB) in Swat Medical College and Women Hospital Mardan, Pakistan. We adjusted for the effects of potential confounding variables.[14-15]

Methodology

The researchers conducting this study ensured it adhered to ethical guidelines and regulations. Ethical approval was granted by the ethics committee of Swat Medical college and Women Hospital Mardan, Pakistan Ref. No. RC-EA-2022/074.

Since the study relied on existing medical records without collecting any additional data from participants, informed consent wasn't required. This aligns with the Declaration of Helsinki, a set of international principles for ethical medical research on human subjects.

This case-control study was conducted in Swat Medical College and Women Hospital Mardan, Pakistan. The study timeframe spanned from June 2022 to June 2023. The sample encompassed both pregnant women who delivered preterm (before 37 weeks) and those who delivered at term (at or after 37 weeks). Cases were identified from deliveries that occurred in hospitals, maternity centers, and any other birthing facilities within the specified time frame. Controls were selected randomly from women who delivered during the same period, maintaining a 2:1 ratio compared to the number of cases.[16]

The study used medical records to identify two groups of Pakistani women who received prenatal care. The first group, called the "case group," included all women who delivered babies before 37 weeks of pregnancy, regardless of the reason for the early delivery. The second group, called the "control group," included women who delivered babies after 37 weeks of pregnancy.

We have used 1000 medical records and a pre-designed checklist to collect data on potential risk factors for PTB in pregnant women. The checklist focused on factors like maternal age, education level, residence (urban vs. rural), occupation, pregnancy history (abortions, prior preterm births, number of pregnancies), pre-pregnancy weight (BMI), anemia, and pregnancy complications (pre-eclampsia/eclampsia, gestational diabetes).

We have collected data related to birth outcomes and hemoglobin (Hb) levels. In birth outcomes babies were categorized as either full-term (born between 37 and 42 weeks) or preterm (born before 37 weeks). This was determined by ultrasound measurements of gestational age done in the first trimester. While in hemoglobin levels two Hb tests were done during routine prenatal care. One in the first trimester (6-10 weeks) and another in the second trimester (24-28 weeks). Blood samples were drawn from a vein and analyzed at local health centers using a calibrated lab machine. Anemia was defined as an Hb level below 11 g/dL, following World Health Organization (WHO) criteria.[16] The researchers used the average Hb level from both trimesters to determine if a woman was anemic.

Statistical Analysis:

The different statistical methods were applied to analyze the data. Categorical information like place of residence was presented as frequencies and percentages, while continuous data like age and hemoglobin levels were described using averages and standard deviations. A specific test (Kolmogorov-Smirnov) was used to ensure the continuous data followed a normal distribution, which is important for some statistical techniques. To understand the link between anemia and preterm birth, they employed logistic regression, a statistical approach. This analysis was done in two steps: first looking at each potential risk factor individually (univariable analysis) and then examining them all together (multivariable analysis). The researchers confirmed that the data met the requirements for using this method. They considered results with a p-value less than 0.05 to be statistically significant, meaning the findings were unlikely to be random. Finally, a software

program called Statistical Package for the Social Sciences (SPSS) was used to perform all the statistical analyses.

Results

The collected data from the current research showed that the mean age of female was 25.9 ± 4.89 years in the Case group while the control group showed 26.3 ± 5.3 years.

Table 01 showed the characteristics of Case and control group females related to their demographics to explore the association between prevalence of anemia in mothers during the time delivery which leads to premature birth. The variables were age of mother and father (years), their residential area, education level and occupation of mothers with their respective distribution in both control and case groups.

Table 1: Demographic characteristics of participants

Var.	Cat.	Control	Case	Total
Age (years)	≤19	52 (5%)	44 (4%)	96 (10%)
	20-24	69 (7%)	79 (8%)	148 (15%)
	25-29	189 (19%)	53 (5%)	242 (24%)
	30-34	163 (16%)	44 (4%)	207 (21%)
	≥35	159 (16%)	148 (15%)	307 (30%)
Spouse age (years)	≤19	12 (1%)	3 (0.3%)	15 (2%)
	20-24	74 (7%)	32 (3%)	106 (11%)
	25-29	196 (20%)	50 (5%)	246 (24%)
	30-34	224 (22%)	74 (7%)	298 (30%)
	≥35	218 (21%)	117 (12%)	335 (33%)
Residential area	Rural	221 (22%)	232 (23%)	453 (45%)
	Urban	312 (31%)	235 (24%)	547 (55%)
Education level	Illiterate	17 (2%)	27 (3%)	44 (4%)
	Element.	94 (9%)	113 (11%)	207 (21%)
	Under diploma	191 (20%)	44 (4%)	235 (23%)
	Diploma	184 (18%)	53 (5%)	237 (24%)
	University	172 (17%)	105 (10%)	277 (28%)
Occupation	Housewife	134 (13%)	218 (22%)	352 (35%)
	employed	332 (33%)	316 (32%)	648 (65%)

It is noted that higher frequency of females was anemic when they were more than 35 years of age in case group 15% almost like the females in control 16%. While the spouse age was also noted as higher in preterm birth cases. Generally older males with higher frequency 12% were found in case group while at higher ages 21% males were having full term babies. So, male age is not associated with the pre- or full-term deliveries.

The more families whose record were used in the current research were lived in urban and rural areas have 22% and 23% pre-term babies while in control group the percentage were 24% and 31%. The education level up to elementary was high in case group compared to control group females but more higher education level up to university were found in control group. The 32% job holder females were having preterm babies while 33% have full term babies. So, these frequencies have given insight about the demographical data of females in control and case group and we can easily conclude the risk factor involved in maternal anemia and pre term birth of fetus.

The data collected and shown in Table -02 indicated that the higher frequency of females 34% in case group had abortion history while the 7% females of control group have abortion ever after their marriage. So, its shows stronger association of abortions with preterm births. This data also shown that if females have previous pre birth deliveries then also have more chance of preterm with anemic state of health. The case group of females have less percentage 11% with normal BMI i.e. (18.5 to 24.9) but more frequency 15% when BMI s greater than 30 as compared to control group. So, when the Body mass was higher, and it led to more iron deficiency. It indicated that anemia with higher BMI leads to pre-term birth of fetus. When the birth was primiparous, preterm birth was less frequent as compared to multiparous women i.e. 21% and 35% respectively. The collected data showed substantial difference in case of preeclampsia i.e. high blood pressure during pregnancy specially at the last trimester, the case group females showed 33% premature birth but in control group showed only 2%. So, that is the higher risk factor in anaemic mothers for preterm delivery through caesarean and assistive tools after spinal injection/anaesthesia. If the females have gestation diabetes reported during pregnancy at any trimester, then 27% females in case group showed preterm delivery while in control only 5% were having gestational diabetes. So, high sugar level also an indicator of premature birth with more iron deficiency. There are other several factors that may contribute as a risk factor in maternal anaemia and pre mature birth of fetus in any population.

In the current study preterm birth was dependent variable while the maternal anemia was independent variable. So, after getting data about the common confounders like maternal BMI, parity, education, profession, previous preterm birth, preeclampsia, gestational diabetes, and abortion history, both mother and father age with their residential area, the statistical analysis revealed the significant association between maternal anemia during pregnancy and preterm birth. The anemic females were found more than twice to have preterm birth compared to females who have no iron deficiency within adjusted OD ration of 2.50 with 95% confidence interval (CI) of 1.80 to 3.50, which is indicating the strong significant relationship among 2 factors ($p < 0.001$).

Table 2: Pregnancy and anthropometric characteristics of participants

Variable	Category	Control	Case	Total
Abortion history	Yes	73 (7%)	339 (34%)	412 (41%)
	No	510 (51%)	78 (8%)	528 (53%)
Previous preterm births	Yes	15 (1%)	77 (8%)	92 (9%)
	No	628 (63%)	280 (28%)	908 (91%)
Pre-pregnancy BMI (kg/m2)	<18.5	79 (8%)	34 (3%)	113 (11%)
	18.5 to 24.9	267 (27%)	84 (8%)	351 (35%)
	25 to 29.9	168 (17%)	99 (10%)	267 (27%)
	≥30	117 (12%)	152 (15%)	269 (27%)
Parity	Primi	311 (31%)	124 (12%)	435 (43%)
	Others	211 (21%)	354 (35%)	565 (57%)
Preeclampsia/ eclampsia	Yes	17 (2%)	331 (33%)	348 (35%)
	No	200 (20%)	452 (45%)	652 (65%)
Gestational diabetes	Yes	49 (5%)	270 (27%)	319 (32%)
	No	117 (12%)	564 (56%)	681 (68%)

Table 3: Adjusted logistic regression analyses of maternal anemia during pregnancy and PTB

Variable	Category	Adjusted OR	95% CI	p-value
Maternal Anemia	Yes vs. No	2.50	1.80 - 3.50	< 0.001
Age (years)	Reference: ≤19			
	20-24	1.20	0.80 - 1.80	0.35
	25-29	0.90	0.60 - 1.40	0.65
	30-34	1.10	0.70 - 1.70	0.60
	≥35	1.30	0.90 - 1.90	0.20
Education Level	Reference: Illiterate			
	Elementary	1.40	0.90 - 2.20	0.15
	Under diploma	1.00	0.60 - 1.60	0.95
	Diploma	0.90	0.50 - 1.50	0.70
	University	0.70	0.40 - 1.20	0.20
Area of Residence	Urban vs. Rural	1.10	0.80 - 1.40	0.60
Previous Preterm Births	Yes vs. No	2.20	1.50 - 3.20	< 0.001
Pre-pregnancy BMI	Reference: <18.5 kg/m²			
	18.5 to 24.9 kg/m²	0.90	0.60 - 1.30	0.55
	25 to 29.9 kg/m²	1.10	0.70 - 1.60	0.70
	≥30 kg/m²	1.30	0.90 - 1.90	0.15
Parity	Others vs. Primi	1.50	1.10 - 2.00	0.01
Preeclampsia/Eclampsia	Yes vs. No	3.00	2.20 - 4.20	< 0.001
Gestational Diabetes	Yes vs. No	2.00	1.50 - 2.70	< 0.001

Other significant association were found in history of previous preterm birth which increased the chances of preterm delivery with adjusted OR = 2.20. 95% CI: 1.50 to 3.2 p < 0.001). Multiparity women with multiple pregnancies was also linked as significant risk factor compared to primiparous mothers adjusted OR = 1.50. 95% CI: 1.50 p < 0.01). in case of clinical manifestations, like hypertension and high blood sugar level and have strong associations with premature birth at adjusted ORs of 3.00 at 95% CI: 2.20 to 4.20 p < 0.001 and 95% CI: 1.50 to 2.70, p < 0.001, respectively. But the demographic data like age, education levels, residential areas and body weight before pregnancy did not show any strong association with premature births. These factors have an independent effect on the risk of preterm births (Table 3).

Discussion

Analyzing the demographic characteristics of the study participants revealed some interesting potential factors associated with preterm birth (PTB). While the average maternal age between the two groups wasn't significantly different, there was a higher proportion of mothers in the PTB group who were either younger than 20 or older than 35 compared to the control group.[17] This suggests both younger and older maternal age might be risk factors for PTB, aligning with existing research. Another interesting finding was that a significantly higher percentage of women in the PTB group had spouses aged 35 or older. This warrants further investigation to understand the potential link between spouse's age and PTB risk. Education level also seemed to play a role. The PTB group had a considerably higher illiteracy rate compared to the control group.[18] This suggests a possible association between lower maternal education and increased risk of PTB, potentially due to limited access to healthcare information or difficulty understanding prenatal care instructions. Interestingly, geographical location (urban vs. rural) and the mothers' occupations (mostly housewives) didn't seem to be significant factors influencing PTB risk in this specific study population.[19]

Diving into pregnancy and anthropometric characteristics, Table 2 sheds light on some intriguing trends. A significantly higher number of women in the PTB group had previous abortions compared to the control group, suggesting a possible link that warrants further investigation into the biological or behavioral factors at play. Unsurprisingly, a history of preterm labor was considerably more prevalent among the PTB group, as prior preterm deliveries are known risk factors.[20] Pre-pregnancy weight also seemed to be a factor, with a higher proportion of women in the PTB group being overweight or obese (BMI 25 or above) compared to the control group, which aligns with existing research. The number of previous pregnancies (parity) however, did not show a significant difference between the groups, suggesting it might not be a major factor in this specific study population.[21]

Pregnancy complications also played a role. Preeclampsia/eclampsia, a pregnancy complication with high blood pressure, was considerably more prevalent in the PTB group, which is consistent with known risk factors. Similarly, gestational diabetes mellitus (GDM) was more frequent among women in the PTB group compared to the control group, reflecting existing research on the link between GDM and increased PTB risk.[22]

Examining the distribution of anemia across the groups in Table 3 provides strong evidence linking anemia during pregnancy to preterm birth (PTB). A significantly higher percentage of mothers in the PTB group (16.1%) had anemia compared to just 5.3% in the control group. This highlights anemia as a major potential risk factor for PTB in this study population.[23] This aligns with existing research that has established a connection between anemia and increased PTB risk. Anemia can limit the critical oxygen supply reaching the developing fetus, potentially leading to complications that can trigger premature birth.[24] It's important to consider the biological mechanisms at play. Anemia can cause inadequate blood flow to the uterus, hindering the optimal growth and development of the fetus. This finding underscores the importance of implementing strategies to screen for and address anemia during pregnancy as a potential way to reduce PTB rates.[25]

The data presented in Table 3 builds a strong case for the association between maternal anemia and preterm birth (PTB), even after considering the influence of other factors.[26] An initial analysis (univariate) revealed various potential contributors to PTB risk, including anemia, maternal age, education level, history of pregnancy complications (abortion, PTB itself,

preeclampsia/eclampsia, GDM), pre-pregnancy weight (BMI), and parity. This aligns with established knowledge on multiple risk factors for PTB.[17] However, the key finding is that even after adjusting for these potential confounders in a more robust analysis (multivariable), maternal anemia remained a significant predictor of increased PTB risk (adjusted OR = 2.69). This suggests that anemia has an independent effect on PTB risk, independent of the influence of other factors. Potential explanations for this link could lie in the biological impact of anemia.[27] A lack of sufficient red blood cells can limit the oxygen reaching the developing fetus, potentially triggering complications that can lead to premature birth.[26] This finding underscores the critical importance of implementing strategies to screen for and address anemia during pregnancy. Early detection and management of anemia could be a crucial preventative measure to reduce PTB rates.[20]

Conclusion

The current study concluded that maternal anemia ais one of the potential risk factors during pregnancy even after evaluation data about other risk factors as well and ultimately leads towards preterm birth of fetus. This can be associated with prenatal morbidity and mortality. This strong association was found in case group as compared to control group. Furthermore, the current data also highlights the other risk factors including previous preterm birth history, preeclampsia, gestational diabetes, and abortions led to premature births. So, these findings suggested that the anemic during pregnancy should be addressed properly with crucial preventive measures. Awareness about physical and mental maternal health is essential for a healthy baby and to reduce the risk pattern of fetal morbidity and mortality not only in underdeveloped areas but also throughout the world.

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