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# Maternal Hemoglobin Levels as a Causative Factor in Incidence of Low Birth Weight Babies: A Public Health Prospective

# Ekarini Daroedono <sup>a\*</sup>, Aurelia Evina Haloho <sup>b++</sup> and Restu Fatimatuzzahra <sup>b++</sup>

<sup>a</sup> Department of Community Medicine, Faculty of Medicine, Universitas Kristen Indonesia, Jakarta, Indonesia. <sup>b</sup> Faculty of Medicine, Universitas Kristen Indonesia, Jakarta, Indonesia.

# Authors' contributions

This work was carried out in collaboration among all authors. Author ED designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors AEH and RF managed the analyses of the study using MS EXCEL, SPSS and MS Powerpoint and both also managed the literature searches. All authors read and approved the final manuscript.

# Article Information

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# ABSTRACT

**Aims:** To analyze some aspects of the maternal and the newborn in the incidence of low birth weight babies (LBWB).

**Study Design:** simple retrospective with cross-sectional design approach. **Place and Duration of Study:** Retrospective data of LBWB obtained from newborn medical record (year 2017-2022) of The Sultan Thaha Saifuddin Tebo Regional Public Hospital, located in Jambi-

++Medical Student;

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<sup>\*</sup>Corresponding author: E-mail: ekarini@uki.ac.id;

Indonesia and analysis conducted in the *Departemen Kedokteran Komunitas* (Community Medicine), the Faculty of Medicine, Universitas Kristen Indonesia, Jakarta Indonesia, between September-November 2023.

**Methodology:** The inclusion criteria focus on all newborn with LBWB that have complete medical record data. The acquired data regarding (1) maternal age, gestational age at the time of giving birth, Hb level prior to delivery, (2) newborn: gender, survivability and birth weight. All respondents will be subjected to statistical analysis using the SPSS programme and Microsoft Excel 2016. The exhibited information consists of data distribution presented in the form of tables and utilising univariate analysis and regression testing.

**Results:** Analysis of 256 LBWB data (122 (47.65%) boys, 134 (52.34%) girls) revealed that in the maternal side mean age 28.54 years old, mean gestational age 36.07 weeks at the time of giving birth and mean Hb level 10.8 gram/dL. In the newborn side viability were 226 (88.33%) viable and mean overall birth weight 1990.2 g. Statistically using Pearson correlation, there is a very weak correlation firstly among maternal Hb count with the neonates primary weight (P = 0.00, r = 0.154) and secondly between gestational age and the birth weight of newborn (P = 0.00, r = 0.000). From the community medicine perspective, Efforts to increase the Hb levels of pregnant women theoretically can be carried out more easily by encouraging and increasing the mother's and also their partners, families and society awareness of carrying out routine antenatal care, encouraging the role of health motivator/local health cadre and conducting Hb examination as simple screening; all of them supported by the government.

**Conclusion:** Maternal low Hb count and gestational age correlate with birth weight of newborn. Further in depth and extensive study needed to explore specific factors contribute to the incidence of anemia in mother who gave birth neonates which have low birth weight (LBW) and their impact to pregnancy.

Keywords: Anemia; pregnancy; antenatal care; health promotion; specific protection; community medicine.

# 1. INTRODUCTION

Birthweight is the primary or first recorded weight of neonates obtained subsequent to birth, which should be measured as soon as possible. Newborn infant should be weighted as soon as possible after its birth and its weight must be documented, ideally weighed within the initial hours after birth [1], aforetime consequential postdeliverv weight deprivation has occurred especially in those with derangement in birth weight [2]. The term LBWB is described as a birth weight of <2500g [3]. This condition of LBWB remains a key global public health matters because its major contribution to neonatal complication and even death in developing countries [1,3].

Epidemiologically, according to UNICEF report, it is estimated 14.7 per cent of all babies born globally in the year 2020, suffered from low birthweight [4]. For each 7 newborns worldwide, 1 suffer from LBW. An elongated analysis of the report on 2017 Indonesian Demographic and Health Survey (IDHS) revealed that 0.67‰ of neonates were actually suffer from LBW [5,6] and this percentage places Indonesia below the Philippines (13.8%) and Myanmar (7.5%) but the same as Cambodia [6]. These unfortunate LBWB were more distinctly possible to suffer from hazardous morbidity that lead to mortality within their first month of life [7,8] and for those who sustained oneself still face prevailing sequalae including a lofty risk of stunted growth [8], more inferior IQ in adulthood [9] late-onset chronic health debilitating conditions such as overweight-obese [10] and also increased risk of future type-2 diabetes with other chronic non communicable illness during adult life [11].

Anemic pregnant women (Hb< 11 g/dL) are at eminent chance of possessing LBWB compared with those normal, non-anemic pregnant women [12]. Anemia is actually a common condition found among pregnant women [13]. Other condition that can contribute for the happening of LBWB is the condition of small for gestational age (SGA). It is characterized by primary birth weight of <10th percentile for their actual gestational age [14]. SGA neonates are divided into 2 groups, namely (1) basically normal infants who are SGA and (2) infants who are SGA because of growth retardation or restriction during pregnancy that resulted in a birth weight lower than predicted superb birth weight [15]. Electronically, there is SGA determination method made available for free [16].

The aim of this study is to characterize LBWB and to determine the correlation between maternal hemoglobin and gestational age with the birth weight.

# 2. MATERIALS AND METHODS

This simple retrospective, cross-sectional study worked on analysis of LBWB primary data with permission letter from the director of the hospital no 445/1970/RSUD/X/2023. Data obtained from newborn medical record (year 2017-2022) of The Sultan Thaha Saifuddin Tebo Regional Public Hospital, located in Jambi-Indonesia and analysis conducted in the Departemen Kedokteran Komunitas (Community Medicine), Faculty of Medicine, Universitas Kristen Indonesia, Jakarta Indonesia, between September-November 2023. The inclusion criteria focus on all newborn with LBWB that have complete medical record data. The acquired data regarding (1) maternal: age, gestational age at the time of giving birth, Hb level prior to delivery, (2) newborn: gender, survivability and birth weight. All respondents will be subjected to statistical analysis using the Statistic Product Service Solution (SPSS) programme, and Microsoft Excel 2016 and MSPowerpoint. The exhibited information consists of data distribution presented in the form of tables and utilising univariate analysis and regression testing.

# 3. RESULTS AND DISCUSSION

In this study, 256 data of newborn with LBWB were analyzed. The amount of LBWB annually (2017-2022) were as follows: 20 (7.8%), 25 (9.8%), 35 (13.7%), 52 (20.3%), 36 (14.1%), and 88 (34.4%). Out of 256 data, 122 (47.65%) were boys and 134 (52.34%) were girls. Statistical analysis revealed that in the maternal side, mean age 28.54 years old, mean gestational age 36.07 weeks at the time of giving birth and mean Hb level 10.8 gram/dL. In the newborn side, viability were 226 (88.33%) viable and mean overall birth weight 1990.26 gram. Detailed data presented in Table 1.

If grouped based on the mother's age range into 16-20 year's old (yo), 21-25 yo, 26-30 yo, 31-35 yo, 36-40 yo, 41-45 yo and 46-49 yo then each group gets as many as 31 (12.1%), 57 (22.2%), 76 (29.6%), 45 (17.5%), 41 (16%), 5 (1.9%) and 1 (0.3%) respectively. The findings from Adugna and Worku [17] from a specialized hospital in northwest Eithiopia revealed that 6% of mothers who gave birth to LBWB were age under 20 years old and this is lower than our findings (12.1%)

while further analysis of 2017 Indonesian and Health Demographic Survey (IDHS) conducted by Wulandari et al [17] found out that pregnant women <20 years had the sharpest LBW percentage (8.9%). These findings indicate that marriage at a young age has the risk of producing offspring with low birth weight. Azinar et al. [18] found in their study that women who got married at very young age (<20 years) actually had a greater risk (1,728 times) to have LBWB compared to those who gave birth in age >20 years old. These findings provide insight into the importance of community antenatal care reproductive programs, regarding health education for women, including anemia, not only pregnant women but even from student days.

Sociological factors such as extreme impoverishment, rural type dwelling, socio-cultural norms and social class in central Africa and southern part of Asia have all been connected with premature onset of marriage [19.20]. Negative effect of premature marriage include: (1) physical and psychological difficulties, e.g., extreme-risk pregnancy followed with risky childbirth, diseases related to sexual relation, mental depression, and perhaps emotional anguish; (2) sudden family issues such as conditional dissatisfaction due to marital milieu, emotional shocking due to the burden of lots of responsibility, diminished of personal independence in family life: (3) worsening social problems such as heavy smoking, risky social behaviors, reduced of access to social and health services, social isolation, reduced access to gain an appropriate and higher educational opportunities; job, eventhough perhaps there is also (4) positive exigency, e.g., accepting full intra-family support, improving living milieu (compared to the premarriage condition), and opportunities for improvement. progression with also empowerment [21,22].

Further breakdown of the data based on the maternal Hb level, showed us that in the range <10 gr/dL, 10-11 gr/dL, >11-12.5 gr/dL and >12.5 gr/dL, respectively were 49 (19.1%), 140 (54.6%), 49 (19.1%) and last but not least 18 (7%). Further statistical analysis to seek for was there any significance of difference in birthweight based on maternal Hb level using Wilcoxon signed rank test showed us there is a significant difference in birthweight based on maternal Hb (P=0.000). Anemia in pregnant women possessed potential harm with deteriorating consequences, both to the mother and the newborn [22,23]. A study conducted by Nainggolan in Sumedang, west

Java-Indonesia found 18.7% anemic pregnant women [24]; while in our data, the prevalence of anemia among mother of LBWB was 189 individual (73.8%). According to Kumari et al. [25] The risk was rely on the anemia stratification and classification, as the strongest relation was found in severe type of anemia with OR, 2.5 and continued by moderate type anemia (OR, 1.11) and the last is the mild type anemia (OR, 0.57). The data suggest that the risk elevated along with the severity of anemia in pregnant women.

Table 1. Distribution of LBWB born in the Sultan Thaha Saifuddin Tebo Regional Public
Hospital, 2017-2022

Category	YEAR											
	2017		2018		2019		2020		2021		2022	
Mother's Age												
Range	n	%	n	%	n	%	n	%	n	%	n	%
16-20	1	5	4	16	5	14,3	8	15,3	3	8,33	10	11,3
21-25	4	20	4	16	9	25,7	12	23,1	7	19,4	21	23,8
26-30	6	30	7	28	10	28,6	16	30,7	13	36,1	24	27,2
31-35	2	10	5	20	6	17,1	7	13,4	6	16,7	19	21,5
36-40	7	35	4	16	5	14,3	5	9,6	7	19,4	13	14,7
41-45	0	0	1	4	0	0	3	5,7	0	0	1	1,1
46-49	0	0	0	0	0	0	1	1,9	0	0	0	0
Total	20	100	25	100	35	100	52	100	36	100	88	100
Baby Gender												
Male	7	35	12	48	17	48,6	31	59,6	14	38,9	41	46,5
Female	13	65	13	52	18	51,4	21	40,3	24	66,7	47	53,4
Total	20	100	25	100	35	100	52	100	36	100	88	100
Maternal Hb												
< 10 gr/dl	3	15	6	24	5	14,3	10	19,2	3	8,3	22	25
10-11 gr/dl	14	70	14	56	22	62,9	23	44,2	21	58,3	46	52,2
11,2- 12,5 gr/dl	2	10	4	16	3	8,5	14	26,9	11	30,6	15	17,1
> 12,6 gr/dl	1	5	1	4	5	14,4	5	9,6	1	2,7	5	5,6
Total	20	100	20	100	35	100	52	100	36	100	88	100
Infant Survival/	Death											
Infant Survival	19	95	22	88	32	91,4	47	90,3	35	97,2	71	80,6
Death	1	5	3	12	3	8,57	5	9,6	1	2,7	17	19,3
Total	20	100	25	100	35	100	52	100	36	100	88	100
Birth Weight												
< 1000 gr	1	5	1	4	0	0	2	3,8	0	0	5	5,6
1100-1500 gr	4	20	3	12	7	20	4	7,6	1	2,78	8	9,1
1510-1700 gr	2	10	1	4	4	11,4	6	11,5	3	8,33	6	6,8
1710-1900 gr	3	15	6	24	4	11,4	3	5,7	3	8,33	11	12,5
1910-2100 gr	4	20	7	28	6	17,1	8	15,3	7	19,4	7	7,9
2110-2250 gr	4	20	2	8	8	22,9	11	21,1	5	13,9	15	17,1
2260-2500 gr	2	10	5	20	6	17,1	18	34,6	17	47,2	36	40,9
Total	20	100	25	100	35	100	52	100	36	100	88	100
Infant Birth Weig	ght Ca											
ELBW	1	5	1	4	0	0	2	3,8	0	0	5	5,6
VLBW	4	20	3	12	7	20	4	7,6	1	2,7	8	9,1
LBW	15	75	21	84	28	80	46	88,4	35	97,2	75	85,2
Total	20	100	25	100	35	100	52	100	36	100	88	100
Small for Gestat												
SGA	16	80	18	72	30	85.7	37	72.5	31	86.1	70	80.4
Non SGA	4	20	7	28	5	14.3	14	17.5	5	13.9	17	19.6
Total	20	100	25	100	35	100	51	100	36	100	87	100

In our opinion, among the existing independent variables, anemia may be one of the condition that can be prevented or at least controlled. In India and many other countries, anemia is commonly seen in all age groups. A condition mainly caused by insufficient iron and or folate in daily meal; where without realizing it, it is possible that daily food does not contain: (1) enough vegetables or fiber (perhaps due to limited availability, financial problem and even personal restriction); (2) restricted meat based food consumption: and (3) unsatisfactory bioavailability of dietary iron from the routine daily diets. All of these three actually must enrich plant-based diets that are presently encouraged among the community as the feasible diets which heralded able to protect people from risk of sedentary, non-communicable the diseases, e.g., cardio-vascular diseases (CVD) and cancer [24-26]. This is the main reason why it is necessary to strengthen the role of community medicine to reach the vulnerable or even marginalized sub population [27]. A communitybased intervention designed for maintaining and even improving case detection and screening effort, referral and up to follow-up commonly found anemia and other non-communicable illnesses amongst pregnant and or postpartum women should be conducted massively through community based antenatal care and health promotion [28-30].

Based on newborn survivability, 226 (88.2%) managed to survive until the babies was discharged from the hospital. Unfortunately, 30 (11.8%) failed. To our opinion, sincere compliment must be given to hospitals that are capable and strive to increase the survivability of LBWB newborns Statistical analysis to seek for difference between survivability and birthweight using Independent-Samples Mann-Whitney U Test (P=0.000). Further analysis based on the condition of SGA found out that out of 256 data LBWB, 204 classified as SGA (79.6%) and 52 (20.4%) not SGA. Statistical analysis using Pearson Chi Square found out that P=0.000, means that there is a correlation between SGA and survivability.

Regarding mortality of LBWB, study conducted by Wondie et al. [31] in Eithiopia found out higher mortality rates, that reach 32.46% (95% CI 29.12% -35.8%) of LBW neonates in the period of 1 week post-partum. The condition of LBWB surely increased the likelihood of mortality in the time of infancy. Newborn with LBW had 200% bigger risk of experiencing mortality during the first year of life compared to the normal children which born with adequate birth weight ( $\beta = 2.02$ . 95% CI: 1.93, 2.12) [32]. Neonates with LBW are prone to various type of comorbidities; this is due to the immaturity on histology, anatomical, properties. biochemical and physiological Worldwide, 60 to 80% of newborn mortality was caused by LBW [33]. Classic data presented by Cartlidge and Stewart [34] showed that neonates with a birthweight ranging from 500 to 699 g, the one year survival rate was about 18%; compared to 70% at birth weight 800 to 999 g, and increased significantly up to 97% at 1300 to 1499 g. The conceivability of survival among LBW ameliorated markedly with surging post-natal age; for example, at 24-25 weeks of gestation it was 35% at birth, then -increased up to 50% at 12 hours post-partum, elevated up to 66% at 1 week after delivery and reached 78% at 4 weeks. Infant mortality was higher in males, but multiple pregnancy actually had no effect. Birth weight is directly related to mortality that might happen during fetal, neonatal, and postnatal period; and future derangement of longstanding growth and also development. LBW alone is the main contributing element to the neonatal mortality [35].

Low birth weight has been defined by WHO as weight at birth of < 2500 grams; and in our study classified as follows: <1000gr, >1000-1500gr, >1500-1700gr, >1700-1900gr, >1900-2100gr, >2100-2250gr and >2250-2500gr with the number of each group in sequence as follows: 9 (3.5%), 27 (10.5%), 22 (8.5%), 30 (11.7%), 39 (15.2%), 45 (17.5%) and 84 (32.8%). Further classification based on birth weight can be grouped into extremely low birth weight (ELBW), very low birth weight (VLBW) and low birth weight (LBW) which the amount in each group respectively: 9 (3.5%), 27 (10.5%) and 220 (85.9%). Statistical analysis to seek for difference between gestational age (data not shown) with birthweight using Wilcoxon signed rank test (P= 0.000). Another statistical analysis conducted on difference between maternal age and birthweight using Wilcoxon signed rank test (P= 0.000). Due to the uniqueness of our data availability, it is difficult to compare with other study regarding the incidence of LBWB, because most of them were come from hospital based data which usually presented as a mix between the normal and abnormal birth weight.

Globally according to WHO that cited by Cutland et al. [36], it is roughly calculated about 15 to 20% of all births, or estimated around 20+ million newborns annually, can be classified as LBWB. Low- to middle-income countries (LMICs) reckon for a disproportionate load of LBWB; >95% of the world's LBWB are come from LMICs [36]. The ultimate obstacles in finding and monitoring the incidence of LBW is that more than half of infants in the LMICs are not weighed at or soon after birth, particularly in South Asia and sub-Saharan Africa, which makes it difficult for epidemiological studies to derive the real scope of the problem [37]. Most population-based survey data often rely only on modeled estimates, with statistical methods to adjust for underreporting and misreporting of birth weight; because epidemiologically the report on this issue is rare and scarce [38].

Once again, from the community medicine perspective, eventhough the scientific proof is insubstantial regarding the usefulness of home visiting care coordination in targeting poor birth result, especially for the LBWB, but the Community should be able to utilizes community health workers or cadres that were supposed to actively screen and identify vulnerable women at risk of acquiring imperfect birth outcomes, followed by connect them to health and social services available in the community, and carefully follow-up each identified health or social issue to a measurable completion [39].

Indonesia actually had established that kind of system nationally, called Posyandu whose main objective is community empowerment. It is a national program rely on community based health

(Upava Kesehatan service Berbasis Masvarakat/UKBM) organized by the community member with full support from the local government, local health officers and community leaders. The activities in Posyandu are known as five-table system, consisting the of: (1) registration, (2) weighing, (3) charging the card to healthy (KMS), (4) health care, and (5) counseling. Posyandu is the leading role in giving the health and nutrition services with efforts to overcome the major health problems to women (specifically pregnant women) and also children [40]. Iron supplementation, antenatal care with health consultation are some government supported activities for pregnant women; even iron supplementation already start very early where it is given for school age girl in order to prevent anemia.

Furthermore, we conducted an in depth analysis regarding three data: birthweight, survivability (viable vs non-viable) and gender; data regarding mean, median and the number of each sub group also added; we presented it in box plot diagram (Fig. 1).

Data presented in Fig. 1 showed us that in the Viable group on both sexes (male or female) have higher birth weight compared to the non - viable group (2067 vs 1408 gr). If studied more deeply based on gender, the male viable group have mean birth weight 2093 gr which was

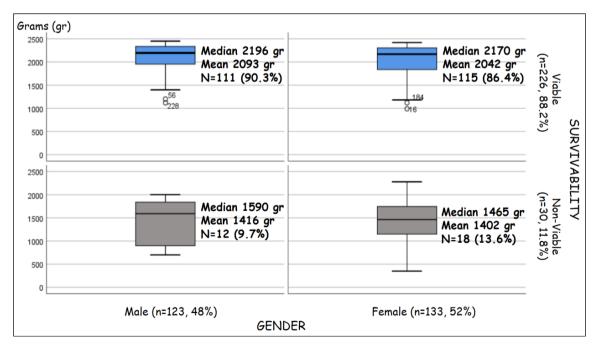


Fig. 1. Box plot diagram regarding birth weight based on gender and survivability

slightly heavier compared to their counterpart the female newborn which viable have mean birth weight 2043 gr. Survivability in both gender is almost the same (Male vs Female = 90.3% Vs 86.4% viable) with mortality slightly higher in the female (9.7% vs 13.6%). The range of birth weight is slightly different between the male vs female newborn. The whisker line is more longer in the female group (compared to the male) and if compared more in-depth, it appears that the nonviable female group has a longer whisker line than the viable ones. Means that, the birth weight range was much greater in the group of women who did not survive.

Statistical analysis to seek for difference between gender based on birth weight using Pearson Chisquare test (P= 0.000). Further statistical analysis for viability based on birth weight resulted P=0.132 which according to Pearson's R showed positive but weak correlation between viability and birth weight.

Unlike our data regarding survivability based on gender, Abdallah [41] in Uganda found out that mortality was higher in male neonates (28.6% vs 13.1%), Ballot [42] in south Africa with male neonates mortality up to 42.7% and data from India reported by Aghai et al. [43] that found out the rate of mortality among neonatal was clearly higher in male neonates (33.2/1,000 live births)

compared to the female group (27.4/1,000, p<0.001). According to Abdallah [41] the incidence of mortality among VLBW subsequent to hospital discharge is remain high. Discharge at weight less than 1200 g clearly not recommended and may not be a safe procedure. Best effort to intercept sepsis and suspected cot death (or sudden infant death syndrome (SIDS)) should be clinically managed and directed appropriately prior to considering early discharge of these infants. All parents that bear children born LBW should be provided with appropriate education regarding specific baby handling, including baby hygiene and all of its utensils, in combination with appropriate medical and support services to minimize the lifelong backlash of poor health condition at birth [44]. Once again, continuous health education must be conducted in order to improve routine and daily low-birthweight infant care practices [45]. This new age of information technology era supposed to be a blessing in disguise for effective health communication (in terms of modality of the media), as has been demonstrated many times during the Covid pandemic, which we believe can also be applied to health education issues for parents of low birth weight babies [46].

Further more, we presented regression from data regarding maternal Hb with the newborn birth weight in Fig. 2.

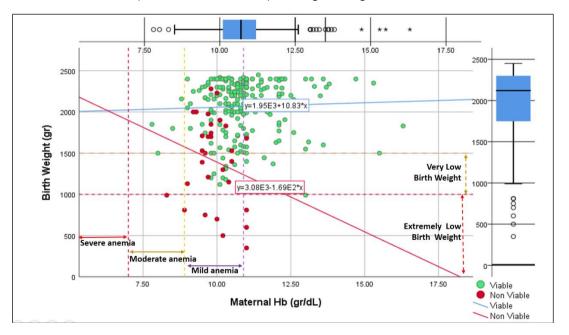


Fig. 2. Linear regression of maternal Hb and newborn birthweight. Viable LBWB newborns were marked with green circle, and non viable ones with red circle. For the viable group, the trend has positive tendency (blue line) while for the nonviable unfortunately has negative tendency (red line)

Data presented in Fig. 2 revealed that out of 226 viable newborn, 86 newborn (38%) had mothers who were not anemic (mean Hb 12.0 gr/dL), 139 newborn had mother with mild anemia (61.5%, mean Hb 10.2gr/dL) and only 1 newborn have mother with moderate anemia (0.4%). While the non-viable group (n=30), 4 had mother with normal Hb level (13.3%, with mean Hb 11gr/dL), 26 (86.7%) had mothers with mild anemia (mean Hb 9.7 gr/dL). In the viable group, higher maternal Hb level positively related with higher newborn birth weight (blue color upward).

Most of the non viable newborn were born to mothers with normal or only mild to moderate anemia; but the downward trend (red line) suggested that the existence of other factors that contribute to the failure to survive in these poor newborn. On contrary, more LBWB babies are fortunate enough to still be able to survive, even though they are born to mothers who suffer from mild to moderate anemia. Further study need to be conduct in order to find the relevant factor that might contribute to survivability or mortality.

Maternal anemia always related to higher risk of disadvantageous events related to birth and or health outcomes [47,48]. In parts of Africa [49,50], south Asia [48,51], and many more LMICs [52] actually had a higher merged anemia prevalence than did other Asian and upper-middle-income countries. Overall, in LMICs, 12% of low birth weight, 19% of preterm births, and 18% of perinatal mortality were related to maternal anemia [47].

LBWB actually as an iceberg phenomenon, that has been linked to several contributing factors, such as maternal [53], socio-demographic [54], physio-biologic [55] and behavioral related maternal competency [56] as well as to the socioeconomic welfare [57], environmental [58], characteristics of specific households food insecuritv situation [59] and common neighborhoods poverty condition [60], and even up to government/state expenditure [61] in combination with level of macro-economic conditions [62].

Once again, our findings suggest the need of good antenatal care (ANC) or maternity care for pregnant women in order to prevent serious complication. The antenatal period presents opportunities for reaching pregnant women with interventions, e.g., health promotion/education, pregnancy check up, vaccination for pregnant women, vitamin and mineral supplementation etc, that may be vital to their health and wellbeing and that of their infants. Receiving antenatal care at least four times increases the likelihood of receiving effective maternal health interventions during the antenatal period. In our opinion, as an effort to address the limitation of this study, it is necessary to carry out further studies regarding the role of ANC patterns in the incidence of pregnancy complications such as LBWB

#### 4. CONCLUSION

Anemic Maternal and gestational age correlate with birth weight of newborn. Further in depth and extensive study needed to explore specific factors contribute to the incidence of anemia in mother who gave birth babies with low birth weight and their impact to pregnancy. Our findings highlight the presence of maternal anemia in the distribution of LBWB. The importance of maternalparental specific health education through multimodel effort (direct face to face health promotion or via social media) with improvement in socioeconomic environments in shaping LBWB, both in urban or rural settings. Implementing contextsensitive interventions quided to improve women's education is highly recommended to reduce the incidence of LBWB.

# CONSENT

It is not applicable.

# ETHICAL APPROVAL

Permission letter was collected from the director of the hospital no: 445/1970/RSUD/X/2023.

# ACKNOWLEDGEMENTS

We sincerely thanked the management of The Sultan Thaha Saifuddin Tebo Regional Public Hospital, located in Jambi-Indonesia that provided us with very important raw data regarding LBWB.

#### **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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