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Below What Hemoglobin Concentration in Pregnancy is there an Increased Risk of Maternal or Fetal Adverse Effects?

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Abstract

Objectives: To identify the lowest hemoglobin concentration (Hb) associated with increased risk of materno-fetal complications.

Material and methods: This cohort study was conducted in the Yaoundé University Teaching Hospital, Cameroon, from March 1st, 2011 to February 28th, 2013. Maternal and fetal outcomes among anemic women (AW) and non-anemic women (NW) were compared. Two hundred and twelve AW (booking Hb <10g/dl) without any chronic diseases, carrying singletons and 212 similar NW (Hb ≥11g/dl) were followed up. Main variables were booking and 36 weeks Hb, complications observed and birth weight (BW). Data were analyzed using SPSS 18.0. Fisher exact test and t-test were used for comparison. Level of significance was P<0.05.

Results: Mean booking Hb was 8.9 ± 1.1 g/dl among AW against 11.7 ± 0.6 g/dl among NW (P<0.001). Complications of anemia in pregnancy in our series [low BW (RR 7, 95%CI 1.6-30.4), pre-eclampsia (RR 3.3, 95%CI 0.9-11.9) and premature delivery (RR 3, 95%CI 0.6-14.6)] occurred frequently when mean 36 weeks Hb was <9g/dl.

Conclusion: Complications were significantly observed when mean Hb was persistently <9g/dl.

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I-Introduction

Anemia in women is defined as hemoglobin concentration (Hb) <12 g/dl. Because of physiologic hemodilution observed during pregnancy, World Health Organization (WHO) defines anemia in pregnancy (AP) as Hb <11 g/dl during first trimester[1,2] or Hb <10.5 g/dl in the second trimester[2]. This definition is not being applied by all authors. For some, AP refers to Hb <10 g/dl during the whole pregnancy.[3,4] Because no studies found any significant maternal nor fetal risk when maternal Hb was ≥10g/dl[5,6] and because hemodilution can start earlier and can be so marked in some pregnant women, AP in our setting is defined as Hb concentration <10 g/dl. When uncorrected, AP is associated with increased risk of intra uterine growth restriction (IUGR), intra uterine fetal death (IUFD), pre eclampsia, preterm delivery, stillbirth and low birth weight (LBW).[6-8]

According to the WHO definition, prevalence of AP varies between 15% and 67% worldwide with one of the highest (30-65%) in sub-Saharan countries[7,9,10] and the lowest rate (15-25%) in developed countries.[2]

Complications of AP depend on its severity. Anemic pregnant women are more prone to death from post partum hemorrhage. It is estimated that 6.37% of maternal death in Africa are anemia attributable maternal mortality whether from direct or indirect cause.[11] Some studies showed that the above mentioned maternal and fetal complications are observed when Hb is less than 9 g/dl.[5] In our country, no study has established above what Hb concentration there are no significant complications of anemia either maternal, fetal or neonatal. The aim of this study therefore was to identify the cutoff point of hemoglobin concentration in pregnancy under which these complications occurred frequently.

II-Material and Methods

This matched cohort study was conducted in the maternity of the Yaoundé University Teaching Hospital, Cameroon, during a two-year period from March 1st, 2011 to February 28th, 2013. During this period, each woman with a singleton and Hb concentration at the first visit (booking) <10g/dl and one control of the same parity with a singleton and Hb concentration ≥11g/dl (standard definition of normal Hb concentration in pregnancy) received immediately after the case were recruited and both followed up till delivery. All women not suffering from any chronic diseases were included and all these women received normal (routine) follow up. Women with disease like chronic hypertension, sickle cell anemia, pre-gestational diabetes were excluded, as well as those who smoked or had gestational diabetes. Between 24 to 28 weeks gestation a fasting blood sugar of >0.92 g/l or values of blood sugar of >1.8 g/dl or >1.53 g/dl one or two hours respectively after oral ingestion of 75 g of glucose were suggestive of gestational diabetes. Eight women with severe anemia (Hb concentration <6 g/dl) received blood transfusion until new Hb concentration was 6 to 7 g/dl. Thereafter, they were prescribed 100 mg of iron supplementation and 1 mg of folic acid daily as other anemic women, while non-anemic women were prescribed 50 mg of iron supplementation and 0.5 mg of folic acid daily. Two women received injectable iron because of intolerance of oral iron therapy. Hb concentration was controlled at 36 weeks gestation. Variables recorded included maternal age at delivery, parity (deliveries at ≥28 completed weeks gestation), gestational age at booking (confirmed by an ultrasound scan performed before 20 weeks gestation), Hb concentration at booking and at 36 weeks gestation, complications observed during pregnancy, gestational age at delivery, birth weight, fetal sex, Apgar score and placental weight. Hb concentration was checked during labor at 35 weeks in four women who had preterm deliveries. Hb concentration was measured

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on automated cell counter (HumaCount 30TS). Before measuring placental weight membranes were removed, the cord sectioned at the placental insertion site and blood drained from the placenta. This study received approval from the institutional ethics committee. Sample size was calculated using the following formula: $N = 2\times(1/1\text{-}f)\times(Z\alpha+Z\beta / P_0\text{-}P_1)^2\times P\times(1\text{-}P)$ where f was the assumed percentage of women who might be lost during follow-up (10%), $Z\alpha = 1.65$, $Z\beta = 1.28$, P_0 the prevalence of LBW (<2500 g at birth) in anemic women (10%), P_1 the prevalence of LBW among non anemic women (2%) and P is $(P_0+P_1)/2$. According to this formula at least 169 women were needed in each group. An informed consent was obtained from each woman. Data were analyzed using SPSS 18.0. Data of anemic pregnant women were compared to those of non anemic pregnant women. Fisher exact test was used to compare categorical variables and t-test to compare continuous variables. We used relative risks with their 95% confidence interval to present the comparison between the two groups. P<0.05 was considered statistically significant.

III- Results

During the study period, we received 235 anemic women (Hb concentration <10g/dl) with singleton pregnancies out of 4150 women giving an incidence of 5.66%. Seven women with gestational diabetes were excluded and 16 women were lost during follow-up. The remaining 212 women were followed up till delivery. Another 212 non anemic pregnant women (Hb concentration ≥11g/dl) were used as control.

Maternal ages at delivery varied between 17 and 45 years among anemic pregnant women (AW) with a mean of 27.9 ± 5.2 years compared to a range of 17 to 41 years with a mean of 28.3 ± 5.2 years among non anemic pregnant women (NW) (P= 0.46). Parities at booking varied between 0 and 5 with a mean of 1.4 ± 1.4 in both groups (P=1).

Mean gestational ages at booking was 19.5 ± 7.3 weeks and ranged from 6 to 34 weeks among AW as against a range of 6 to 29 weeks with a mean of 17.8 ± 4.9 weeks among NW (P=0.0051).

Hb concentration at booking varied between 3.4 and 9.9 g/dl with a mean of 8.9 ± 1.1 g/dl among AW as against a range of 11.0 to 14.1 g/dl with a mean of 11.7 ± 0.6 g/dl among NW (P<0.0001) (Table 1). Eight women had severe anemia (Hb concentration <6g/dl), 11 had moderate anemia (Hb concentration: 6 to < 8 g/dl), and 193 mild anemia (Hb concentration: 8 to <10g/dl).

Table 1: Distribution of Hb concentration at booking among anemic pregnant women.

Hb level (g/dl)	Number (%)
3 to <4	3 (1.4)
4 to <5	3 (1.4)
5 to <6	2 (1.0)
6 to <7	2 (1.0)
7 to <8	9 (4.2)
8 to <9	59 (27.8)
9 to <10	134 (63.2)
Total	**212** (100)

Mean Hb concentration at 36 weeks gestation was 10.8 ± 1.2 and varied between 4.7 and 13.3 g/dl among initially AW compared to a range of 11.0 to 13.5 g/dl with a mean of 11.9 ± 0.6 g/dl among NW (P<0.0001) (Table 2). Three women with Hb concentration <8g/dl at 36 weeks received blood transfusion until new Hb value was ≥10g/dl.

Gestational age at delivery varied between 35 and 43 weeks with a mean of 39.9 ± 1.6 weeks among AW as against a range of 36 to 42 weeks with a mean of 39.6 ± 1.3 weeks among NW (P=0.07). Preterm deliveries were more observed among AW (six cases against two) (RR 3, 95%CI 0.6-14.6, P=0.28).

Table 2: Distribution of Hb concentration at 36 weeks among initially anemic women.

Hb at 36 weeks in g/dl	Number (%)
4 to <8	3 (1.4)
8 to <9	15 (7.1)
9 to <10	24 (11.3)
10 to <11	56 (26.4)
11 to <12	80 (37.8)
12 to <14	34 (16.0)
Total	**212 (100)**

Mean birth weight of babies delivered by women whose Hb <9g/dl at 36 weeks (n=18) was lower than that of babies delivered by non-anemic (Hb ≥11g/dl) pregnant women (n=212) (2742.1 ± 585.1 g vs 3243.5 ± 328.2 g, P<0.0001).

Outcome of pregnancy among AW whose Hb <7g/dl at 36 weeks (n=3) was mainly marked by LBW, when compared to NW (n=212) (2366 ± 116 g vs 3243.5 ± 328.2 g, P<0.0001).

Mean birth weights were significantly higher among initially anemic women than among controls. Indeed, birth weights ranged from 1877 to 4500 g with a mean of 3328 ± 496.7 g among AW and a range from 2327 to 4150 g with a mean of 3243.5 ± 328.2 among NW (P=0.039). In relation to fetal sex, among anemic pregnant women male fetuses had higher birth weight (≥3500 g) than female fetuses (50/101 versus 27/111) (RR 2, 95%CI 1.3-2.9, P=0.0004).

Newborns were males in 101 cases (47.6%) in AW as against 99 (46.7%) in NW (P=0.88). Babies with birth weight <2500 g were predominantly found among AW (14 cases against 2) (RR 7, 95%CI 1.6-30.4, P=0.003).

Apgar scores varied between 3 and 10 with a mean of 7.9 ± 1.0 among AW as against a range of 4 to 10 with a mean of 8.0 ± 1.0 among NW at the first minute (P=0.39) while at the 5th minute, it varied between 5 and 10 with a mean of 9.2 ± 0.9 among AW as against a range of 6 to 10 with a mean of 9.2 ± 0.8 among NW (P=0.95). Poor Apgar score (<7) at first minute was noticed among 18 cases in the anemic group as against 16 in the non anemic group (P=0.85) while poor Apgar score at 5th minute was noticed among four cases in the anemic group as against five in the non anemic group (P=0.99).

Complications noticed during pregnancy were LBW, premature delivery and pre-eclampsia (Table 3). Fourteen cases of LBW (6.4%), including six cases of premature delivery, were observed in the anemic group (mean Hb concentration 8.9 ± 1.9) and only two (0.9%) among the controls (RR 7, 95%CI 1.6-30.4, P=0.003). Ten cases of pre-eclampsia (4.7%) were observed in the anemic group (mean Hb concentration 8.5 ± 0.8) as against three (1.4%) in the control group (RR 3.3, 95% CI 0.9-11.9, P=0.04). Premature deliveries were also noticed amongst six women among AW (2.8%) as against two (0.9%) in the NW (RR 3, 95%CI 0.6-14.6, P=0.28). Among pregnant women who were anemic at booking, mean Hb concentration was 8.7 ± 0.9 at 36 weeks for women (n=6) who delivered before 37

Table 3: Maternal and fetal complications.

Complications N (%)		Anemic pregnant women (n=212)	Non anemic pregnant women (n=212)	RR	95%CI	P
Maternal	Pre-eclampsia	10 (4.7)	3 (1.4)	3.3	0.9-11.9	0.04
Fetal	Prematurity	6 (2.8)	2 (0.9)	3	0.6-14.6	0.28
	Low birth weight	14 (6.6)	2 (0.9)	7	1.6-30.4	0.003
Total		**30 (14.1)**	**7 (3.3)**	**4.2**	**1.9-9.5**	**<0.0001**

complete weeks against 10.8 ± 1.2 for those who delivered at 37 weeks or above (n=206) (P<0.0001).

Placental weights varied between 225 and 820 g with a mean of 499.7 ± 101.4 g among AW as against a range of 301 to 520 g with a mean of 408.5 ± 45.2 g among NW (P<0.0001). Mean placental weight for women (n=78) with booking Hb <9g/dl was 526.4 ± 99.9 g versus 408.5 ± 45.2 g for controls (P<0.0001) and that of women (n=134) with booking Hb of 9 to <10g/dl was 483.0 ± 99.1 g versus 408.5 ± 45.2 g for control (P<0.0001).

IV- Discussion

The incidence of anemia (Hb concentration <10g/dl) in our study (5.66%) is lower than that of 8.6% reported in Israel.[3] Gestational age at booking for AW (19.5 weeks) was higher than that of NW (17.5 weeks) (P=0.0051). Some of these anemic women started consultation so late that hemodilution might be so advanced aggravating pre-existing anemia or could have been solely responsible for the anemia (physiologic).

Among AW, mean Hb concentration was 8.9 ± 1.1 g/dl at booking as against 10.8 ± 1.2 g/dl at 36 weeks (P<0.0001). Iron therapy in pregnancy has been shown to improve Hb concentration among anemic women.[12,13] Although iron therapy improved maternal Hb concentration at term, term Hb concentration was significantly lower among AW than among the control group despite treatment with iron and folic acid (P<0.0001). This signifies that, to reduce the prevalence of anemia in pregnancy at term, anemia should be treated before women get pregnant.

When we considered gestational age at delivery, women with booking Hb concentration <10g/dl had increased risk of preterm delivery than those with Hb concentration ≥11g/dl (RR 3, 95%CI 0.6-14.6). This is due to the fact that anemia with resulting hypoxia can induce maternal and fetal stress, which stimulates the synthesis of corticotropin-releasing hormone (CRH). Elevated CRH concentrations are a major risk factor for preterm labor, pregnancy-induced hypertension and eclampsia, and premature rupture of the membranes.[14] Our rate of premature delivery among anemic pregnant women (2.8%) was lower than that of 4.1% reported by others.[8] Furthermore, our rate of pre-eclampsia/ eclampsia (4.7%) was also lower than that of 7.3% observed elsewhere.[15]

In our series, the rate of IUGR appreciated by the term born LBW rate (8/212 or 3.8%) was similar to than that reported elsewhere.[6] Our study showed that when booking Hb was between 7 and 8 g/dl, women taking high dose iron and folic acid therapy had similar birth weights as NW (P=0.575). But when booking Hb was <7g/dl there was significant reduced BW among AW (P<0.0001). This shows that despite high dose of iron and folic acid therapy, anemia was so severe that there was a negative impact on fetal growth. Contrary, when booking Hb was between 8 to <9 g/dl there was significant increased BW among AW (P=0.0306). This significant increase in BW was also observed when booking Hb was 9 to <10 g/dl. This increase in BW among AW taking high dose iron and folic acid when booking Hb was 8 to <10 g/dl can be explained by the fact that a well functional big placenta associated with a normalized Hb value when the fetus is still growing might contribute to increased birth weight as suggested by some authors.[13]

Mean birth weight for AW with 36 weeks Hb concentration <9g/dl was lower than that observed among NW (P<0.0001). Other studies showed that persistent severe anemia in pregnancy was associated with increased risk of IUGR and LBW.[6-8] Mean placental weight for women with booking Hb <9g/dl was higher than that found among women with booking Hb of 9 to <10 g/dl (526.4 g vs 483.0 g). Although increased placental weight was observed among all anemic pregnant women, women whose Hb concentration was

<9g/dl were more at risk of significant increased placental weight. This might be explained by the fact that placental hyperplasia and hypertrophy increase with severity of anemia. Some authors found that placenta hypertrophy was significantly found among women with Hb <8.0g/dl.[16]

Main complications observed during pregnancy were LBW, pre-eclampsia and preterm birth. Mean Hb concentration at booking for women with LBW, pre-eclampsia and premature deliveries was usually <9g/dl. Women with Hb concentration ≥9g/dl had low risk, as well as women with Hb at booking ≥11g/dl. Low complication rate has already been noticed among women whose Hb concentration was ≥9g/dl.[5,6] Minimal Hb concentration that is accepted among pregnant women varies so widely according to authors that we are asking ourselves what should be the lower limit of normal hemoglobin concentration in pregnancy.

V- Conclusion

This study found that maternal and fetal adverse effects of anemia in pregnancy are commonly observed when mean Hb concentration is persistently <9g/dl. Nevertheless, we think that a Hb value <10g/dl should not be tolerated because antepartum hemorrhage or hemorrhage during vaginal or cesarean delivery is unpredictable and might be life threatening in women whose Hb concentration is 9g/dl or slightly above.

Conflict of interest: The authors have none to declare.

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