Maternal haemoglobin and premature child delivery

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العلاقة بين نسبة الهيموغلوبين في دم الأمهات وبين ولادة أطفال مبتسرين

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خلاصة: أجريت دراسة مستقبلية على 921 حملاً منخفض المخاطر، وذلك لمعرفة تأثير فقر الدم (حيث مستوى الهيموغلوبين أقل من 11 غرام/ ديسيلتر) أثناء الحمل على حدوث الولادات المبتسرة. وتم قياس مدى الارتباط بين فقر الدم وبين الابتسار عند ثلاثة مستويات مختلفة للهيموغلوبين، وذلك في وقت مبكر من الحمل وخلال الأثلوث الثالث. ووجد أن خطر حدوث الابتسار كان أعلى مع مستوى هيموغلوبين أقل من 9 غرام/ ديسيلتر في مرحلة الحمل المبكر. وجاء بعد ذلك مستوى الهيموغلوبين الذي يقل عن 10 غرام/ ديسيلتر أثناء نفس المرحلة. وسجل أدنى احتطار أثناء الأثلوث الثالث عندما كان مستوى الهيموغلوبين أقل من 10 غرام/ ديسيلتر. وبإجراء تحليل الانحدار اللوجستي عديد المتغيرات، وجد أن الهيموغلوبين هو أهم عوامل التكهن بالابتسار وذلك بعد ضبط عوامل التشويش الأخرى. وعند تطبيق معادلة التكهن اللوجستي، وجد أن المرأة التي لديها جميع عوامل الاختطار المهمة والتي يشملها التحليل المتعدد المتغيرات، كان لديها احتمال بنسبة 72% لأن تضع مولوداً مبتسراً.

ABSTRACT The effect of anaemia (haemoglobin <11 g/dl) during pregnancy on preterm delivery was prospectively studied in 921 low-risk pregnancies. The association between anaemia and prematurity was measured at three different haemoglobin levels, early in pregnancy and during the third trimester. The risk of prematurity was higher with haemoglobin <9 g/dl in early pregnancy, followed by haemoglobin <10 g/dl during the same period; the least risk was recorded during the third trimester when haemoglobin was <10 g/dl. In multivariate logistic regression analysis, haemoglobin was the most important predictor of prematurity after controlling for other confounders. When applying the logistic predictive equation, a woman with all the significant risk factors included in the multivariate analysis had a 72% probability of giving birth to a preterm baby.

L'hémoglobine de la mère et l'accouchement avant terme

RESUME L'effet de l'anémie (hémoglobine < 11g/dl) durant la grossesse sur l'accouchement avant terme a fait l'objet d'une étude prospective portant sur 921 grossesses à faible risque. L'association entre l'anémie et la prématurité a été évaluée à trois taux d'hémoglobine différents, au début de la grossesse et durant le troisième trimestre. Le risque de prématurité était plus élevé avec un taux d'hémoglobine < 9 g/dl au début de la grossesse, suivi par un taux d'hémoglobine <10 g/dl durant la même période; le moindre risque a été enregistré durant le troisième trimestre de grossesse lorsque le taux d'hémoglobine était inférieur à 10 g/dl. Dans l'analyse de régression logistique multivariée, l'hémoglobine était le facteur prédictif le plus important de la prématurité après contrôle d'autres facteurs de confusion. Lorsque l'équation prédictive logistique était appliquée, une femme présentant tous les facteurs de risque significatifs inclus dans l'analyse multivariée avait une probabilité de 72% de donner naissance à un prématuré.

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Introduction

Preterm births continue to be the leading cause of perinatal and postnatal mortality and morbidity, especially in developing countries where health facilities are limited [*1*,*2*]. Prematurity includes two distinct types of infant; infants who are small because they are born early and infants who are born at or near term but are small because their growth was retarded. The term prematurity has been replaced by low birth weight to describe an infant weighing less than 2500 g and preterm to characterize a baby born before 37 weeks of gestation [*3*]. A number of risk factors for preterm birth have been identified by many authors [*3*–*7*].

The role of maternal anaemia in the pathogenesis of preterm birth is a controversial matter. While some researchers have found a strong association between low maternal haematocrit and the occurrence of preterm births [*8*,*9*], others have not found anaemia to be an important predictor of prematurity [*3*,*10*,*11*]. This study was conducted to investigate the relationship between maternal haemoglobin early in pregnancy and during the third trimester and the delivery of preterm babies among low-risk pregnancies.

Subjects and methods

A prospective study was carried out in Alexandria from November 1996 to July 1997. Out of the six districts of the city, four were randomly chosen to be included in the study. From each one, a maternal and child health (MCH) centre was selected to represent the district. The selection was based on the following criteria: availability and completeness of the medical records, willingness of the managers to participate, number of pregnant women attending the centre and the availability of medical facilities and equipment, especially those for measuring haemoglobin level and urine analysis.

In all, 921 women with singleton deliveries were interviewed and had their medical records reviewed. Women were eligible to be included in the cohort for this analysis if they fulfilled the following criteria.

- There was no vaginal bleeding in the third trimester (such bleeding could lead to conditions associated with prematurity and low haemoglobin).
- The pregnancy was not artificially interrupted before 37 weeks of gestation (to ensure the occurrence of spontaneous preterm delivery and not complications of pregnancy requiring early delivery).

There were 17 women excluded as a result of twin pregnancy or because medical intervention had led to premature delivery. In addition, 72 women were lost to follow up; most of them were living outside Alexandria or their addresses could not be reached. Information was obtained by personal interview, review of the women's medical records and home visits in order to confirm the birth date for those women who delivered outside the centre and had not registered the baby's birth date in the records. Data were collected about age, socioeconomic status, previous obstetric history, history of the present conception, medical history and anthropometric measurements. Urine analysis was performed for detection of sugar, albumin and pus cells. Haemoglobin level was assessed using the cyanmethaemoglobin method during the first visit, whether it occurred in the first or second trimester, then again at the beginning of the third trimester and then at each visit until delivery. The two measurements used for analysis were the one taken

Table 1 **Crude odds ratios and confidence intervals for different levels of haemoglobin**

Haemoglobin level (g/dl)	Early in pregnancy			Third trimester		
	OR	95% CI	P	OR	95% CI	P
<11	1.6	0.94–2.61	NS	1.4	0.88–2.51	NS
<10	2.7	1.48–4.91	< 0.001	2.09	1.12–3.87	< 0.01
<9	4.3	1.64–11.29	< 0.001	0.86	0.11–6.72	NS

OR = odds ratio CI = Confidence interval NS = not significant

at the first visit and the last one taken before delivery. The date of the last menstrual period was taken from the records, confirmed by the mother and verified by ultra songraphy only for women who were not sure of their dates.

The crude association between haemoglobin and prematurity was first examined and then logistic regression analysis was performed to study the association between maternal haemoglobin and preterm delivery. Multivariate logistic regression analysis was chosen over multifactorial discriminant analysis as logistic regression does not assume a normal distribution for categorical independent variables. Three models were constructed with forward stepwise selection for three haemoglobin levels, <9 g/dl, <10 g/dl and <11 g/dl. The initial model contained haemoglobin alone as a single predictor of prematurity. Subsequently, additional logistic regression analyses were performed to determine the role of maternal haemoglobin in prematurity prediction when controlling for other potential confounders. In all analyses, the odds ratio (OR) and 95% confidence intervals (CI) were determined.

Results

The total number of women included in the analysis were 832. Two outcome categories were identified based on the length of gestation: preterm births (63, 7.6%), delivered spontaneously before the 37th week of gestation, and term births (controls) delivered at 37 weeks gestation or later (769, 92.4%). The crude association between prematurity and haemoglobin levels of <11 g/dl, <10 g/dl and <9 g/dl, early in pregnancy and during the third trimester is shown in Table 1. There was a negative association between haemoglobin level and prematurity where the risk of prematurity increased when the haemoglobin level was <9 g/dl (OR – 4.3, CI 1.64–11.29), followed by the risk when haemoglobin was <10 g/dl (OR = 2.7, CI 1.48–4.91) in early pregnancy. The least risk (OR = 2.09, CI 1.12–3.87) occurred with haemoglobin <10 g/dl during the third trimester. No significant association was detected with haemoglobin <11 g/dl for both periods or <9 g/dl during the third trimester.

The distribution of demographic characteristics of pregnant women according to cases and controls is shown in Table 2. The factors included contain the potential confounders of the association between haemoglobin and prematurity. A series of stepwise forward logistic regression analyses were performed starting with haemoglobin as a single predictor of prematurity. Then hierarchical combined regression models were developed, where all potential

Table 2 **Distribution of different factors (confounders) among cases and controls**

Variable	Term (n = 769) %	Preterm (n = 63) %
Age (years)		
<20	5.5	4.9
20–35	88.2	90.2
>35	6.3	4.9
Weight (kg)		
<60	8.1	15.9
61–75	41.4	47.6
>75	50.6	36.5
Height > 160 cm	59.3	64.5
Early vaginal bleeding	6.9	11.1
Previous preterm birth	3.0	4.9
Previous abortion	14.8	11.1
Previous child death	4.8	3.2
Parity > 3	27.2	25.4
Urinary tract infection	6.9	6.3
Family history of preterm births	6.6	15.9
Late antenatal care	46.9	65.5
Low maternal education	72.1	68.3
Low paternal education	65.8	65.6

confounders (listed in Table 2) were included in the models to control for them and to detect the importance of haemoglobin as a predictor of prematurity after adjusting for the effect of other independent variables.

Three separate models were developed for the three significant haemoglobin levels shown in Table 1. Five variables remained significantly associated with the outcome and they were the same in the three models, namely: haemoglobin level, positive family history, weight <60 kg, no early antenatal care and early vaginal bleeding. The OR and CI seen in Table 3 indicate that, even after controlling for confounders, haemoglobin was still a strong predictor of prematurity. On the basis of R statistics (similar to correlation coefficients and which measures the contribution of each independent variable for prediction of the dependent one), it appears that most of the variations in the occurrence of prematurity can be explained by haemoglobin changes, i.e. haemoglobin ranked as the first predictor early in pregnancy and the third during the third trimester. It is interesting to note that the strength of association between haemoglobin and prematurity was little altered after adjusting for other confounders.

The −2 loglikelihood (−2 LL) and the percentage of cases correctly classified for the three models were respectively: 412.79, 92.46%; 410.71, 92.37%; 413.56, 92.36%. One of the important benefits of logistic regression is that it allows the risk of occurrence of the dependent variable (preterm delivery) to be predicted using the logistic regression equation:

Probability of dependent variable =

$$\frac{1}{1+\exp\left(-\left(\alpha+\sum_i^p \beta_i x_i\right)\right)}$$

where:
α is the constant; and
β_1 to β_p are the respective coefficients of the variables which are significantly associated with the dependent variable.

When applying this equation to our model, the probability of a woman having a premature baby when her haemoglobin was <10 g/dl, she weighed <60 kg, with a family history of prematurity, with early vaginal bleeding and with late antenatal care is 72%, calculated from the equation above using the values given in Table 3 (model 1).

Table 3 **Adjusted OR and CI for preterm delivery from the three final models of significant haemoglobin levels**

Model	β	OR	95% CI	R statistics	*P*
Model 1 (Hb < 10 g/dl in the third trimester)	0.711	2.03	1.08–3.83	0.0905	<0.01
Positive family history	1.013	2.75	1.30–5.84	0.106	<0.01
Weight < 60 kg	0.992	2.69	1.20–6.04	0.0900	<0.05
No early antental care	0.708	2.03	1.17–3.50	0.1007	<0.05
Early vaginal bleeding	0.977	2.65	1.08–6.53	0.075	<0.05
Model 2 (Hb < 10 g/dl in early pregnancy)	0.970	2.63	1.48–4.71	0.128	<0.005
Positive family history	1.05	2.86	2.12–3.64	0.111	<0.01
Weight < 60 kg	1.08	2.94	2.25–3.73	0.105	<0.01
No early antenatal care	0.703	2.02	1.44–2.53	0.099	<0.05
Early vaginal bleeding	0.833	2.3	1.45–3.26	0.56	<0.05
Model 3 (Hb < 9 g/dl in early pregnancy)	1.387	4.01	2.28–7.03	0.1019	<0.005
Positive family history	1.116	3.05	2.28–3.75	0.1012	<0.01
Weight < 60 kg	1.02	2.79	1.96–3.57	0.098	<0.05
Late antenatal care	0.694	2.0	1.45–3.12	0.097	<0.05
Early vaginal bleeding	0.879	2.4	1.49–3.32	0.051	<0.05

OR = odds ratio CI = confidence interval β = type 2 risk Hb = haemoglobin

Discussion

Anaemia is quite prevalent among women in developing countries, especially during the child-bearing years. Two recent studies conducted in Upper Egypt [*12*] and Beheira Governorate [*13*] have indicated an anaemia level among pregnant women of 73.5% and 48.8% respectively. In the present study, the percentage of pregnant women with haemoglobin level < 11 g/dl was 49.5%.

Many recent studies have not taken anaemia into account as an important predictor of prematurity [*14,15*]. Indeed, Forest et al. considered that haematocrit and serum albumin levels could not be used as useful predictors of preterm delivery [*16*]. Furthermore, Klebanoff et al. reported that anaemia was not associated with preterm delivery, and that the physiological rise of haematocrit in the last trimester could lead to a spurious association between preterm delivery and anaemia [*11*]. However, it is uncertain to what extent these observations from industrialized countries apply to developing ones, where anaemia is much more prevalent and severe.

We found a strong association between maternal anaemia and the occurrence of preterm births and the risk increases with decreasing Hb levels. The risk of prematurity was greatest with haemoglobin <9 g/dl in early pregnancy (first trimester and first few weeks of the second), followed by the risk with haemoglobin <10 g/dl during the same period. Then the risk decreased with haemoglobin <10 g/dl during the third trimester. The risk of prematuriy was not significant when haemoglobin was 11 g/dl in either trimester and also <9 g/dl during the third trimester. The latter could be explained by the fact that 24 women had hae-

moglobin <9 g/dl early in pregnancy but with continuous treatment only four cases remained so during the third trimester and of these only one case was premature.

Mavalanker et al. [*17*], Adams et al. [*18*] and Lieberman [*8*] have all reported an increased risk of preterm births with decreasing haematocrit levels. The findings of our study agree with those of Frederick and Anderson who found that the risk of prematurity increased at very low haemoglobin levels (<9 g/dl) [*19*]. Most studies have focused on anaemia in the third trimester and have not considered haemoglobin levels in early pregnancy with regard to prematurity. We measured the changes that occurred in haemoglobin level during the first trimester and early weeks of the second and related these changes to preterm delivery. We found that the risk of prematurity increased with severe anaemia (haemoglobin <9 g/dl). These results concur with those of Murphy who found that high as well as low haemoglobin during the first and second trimesters were associated with increased risk of perinatal death, preterm delivery and low birth weight [*20*].

It should be noted that anaemia is a function of plasma volume and red cell mass, both of which increase during pregnancy, but the increase in plasma volume is proportionately greater than the increase in red cell mass [*11*]. Low haematocrit late in pregnancy might result from a failure of the expansion of red cell mass or an unusually large increase in plasma volume. A number of mechanisms could account for why anaemia is a risk factor for adverse pregnancy outcome. Low haemoglobin or haematocrit might be a marker of some other risk factors such as poor nutrition, infection or others. Such factors could independently cause prematurity. Also, low haematocrit could lead to decreased oxygen delivery to the fetus [*8*].

We conclude that anaemia is strongly associated with premature delivery and it represents one of the important independent factors for prediction of prematurity. Fortunately, anaemia is a treatable condition and can be easily combated but there are also other risk factors which should be dealt with. More research should be conducted to include factors outside the medical model, such as social support, stress and other lifestyle elements. All of these models should be tested in order to identify and confirm the populations at risk and thus improve antenatal management.

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