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Iron Deficiency Anemia in Pregnancy: Subgroup Analysis from Riyadh Mother and Baby Multicenter Cohort Study (RAHMA)

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Abstract:

OBJECTIVES: The objective of the study was to estimate the prevalence and risk factors of anemia among pregnant women in Riyadh and to examine its association with adverse pregnancy outcomes.

METHODS: This study is a subgroup analysis from Riyadh mother and baby multicenter cohort study. Participants were grouped into four groups according to hemoglobin level: nonanemic (≥ 11.0 g/100 ml), mild (10–10.9 g/100 ml), moderate (7.0–9.9 g/100 ml), and severe anemia (<7.0 g/100 ml). Regression analyses were conducted to extrapolate the predicted probability (PP) for pregnancy outcomes.

RESULTS: Out of 10,600 participants, 3261 (30.76%) were anemic; 1729 (16.3%), 1520 (14.3%), and 12 (0.1%) had mild, moderate, and severe anemia, respectively. The odds of anemia was higher in younger mothers (odds ratio [OR] = 0.94, confidence interval [CI]: 0.91–0.94) and in primiparous (OR = 1.01, CI: 0.90–1.14), while attendants of antenatal care and those who received iron supplements were less likely to be anemic (OR = 0.93, CI: 0.82–1.06) and (OR = 0.92, CI: 0.77–1.09), respectively. There was a significant increase in the odds of lower APGAR with the decreased hemoglobin; an increment of maternal hemoglobin by 1 g/100 ml decreased the likelihood of APGAR scores <7 by 9% (OR = 0.91, CI: 0.83–0.99). The PP showed a decrease in preterm birth (PTB) rate from 8% (CI: 6%–9%) to 6.5% (CI: 5%–8%), low birth weight (LBW) rate from 12% (CI 10%–13%) to 11% (CI: 9%–12%), stillbirth rate from 1.3% (CI: 0.7%–2.1%) to 1.1% (CI: 0.7%–1.6%), and maternal admission to intensive care unit (ICU) from 0.8% (CI: 0.2%–1.5%) to 0.2% (CI: 0.06%–0.4%), with increase of maternal hemoglobin from 7 g/100 ml to 15 g/100 ml.

CONCLUSION: More than a third of the pregnant women in Riyadh had mild-to-moderate anemia. The odds of anemia increased in primipara, younger mothers, and those without antenatal care or iron supplementation. PP showed that anemia is associated with low APGAR scores, LBW, PTB stillbirth, and maternal admission to ICU.

Keywords:

Maternal anemia, pregnancy outcomes, Saudi Arabia

Introduction

Worldwide, anemia is the most common blood disorder. It accounts for nearly 9% of the total global disability burden from all conditions.^[1] Iron deficiency anemia (IDA) is the most prevalent type; it is

estimated that more than 62% of anemia cases worldwide are due to iron deficiency.^[1] In 2011, more than 32 million pregnant women were categorized as anemic of whom almost a million had severe anemia.^[2] The World Health Organization (WHO) estimated that 40% of the pregnant women worldwide are anemic.^[3] The prevalence of anemia among pregnant women in Africa, South Asia, and

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the Middle East was estimated to be 56%, 52%, and 30%, respectively, in comparison to a prevalence of 22% in high-income regions.^[2]

Dietary iron is required for the synthesis of proteins, particularly hemoglobin and myoglobin, which are responsible for the transport of oxygen throughout the body.^[4] Typically, iron is well conserved and is only readily lost during bleeding, menstruation, or pregnancy.^[4] One of the primary causes of IDA in pregnancy is a decreased dietary intake of iron and failure to meet the increased iron needs associated with pregnancy.^[3,4] Other causes of anemia include malaria, which is a primary cause of anemia in the east and west Africa. Nevertheless, inherited hemoglobinopathies, such as sickle cell anemia and thalassemia, are one of the top three global causes of anemia in pregnancy. In addition, low socioeconomic status and other nutritional deficiencies such as folate and vitamins A-E are all risk factors for anemia.^[3]

Severe anemia in pregnancy has been associated with adverse maternal and pregnancy outcomes including preterm birth (PTB), low birth weight (LBW), and perinatal and neonatal mortality.^[5] Postpartum anemia is associated with increased breathlessness, tiredness, reduced immunity, and sepsis.^[6] Although the aforementioned adverse effects are more prevalent with severe anemia, nevertheless, moderate anemia in pregnancy is associated with considerable adverse pregnancy outcomes.^[7]

Most of the studies published on anemia in pregnant women in Saudi Arabia are either outdated or include a small number of participants.^[8,9] In a study published in 1994 by Mahfouz *et al.*, the prevalence of anemia in pregnant women in the Asir region was 31.9%. In this study, increased prevalence was associated with younger age, multiparity, lower education levels, and shortened interpregnancy intervals.^[8]

The objectives of this study are (1) to estimate the prevalence and risk factors of anemia among pregnant women in Riyadh and (2) to examine its association with adverse pregnancy outcomes.

Methods

Study design and participants

RAHMA is a large multicenter cohort study conducted in three hospitals in the city of Riyadh in Saudi Arabia selected by stratified cluster random sampling procedure. All Saudi women and their babies who delivered in participating hospitals were eligible for recruitment. Recruitment of the cohort commenced in the participating hospitals in November 2013 and data

collection concluded in March 2015. The study recruited 14,568 Saudi pregnant women and their newborns. The data from the study formed a foundation for a pregnancy and childbirth database with the intention of investigating the risk factors for pregnancy and adverse perinatal outcomes.

Laboratory and obstetric data, mother and infant medical records, and ultrasound reports were retrieved to maximize the utilization of routinely gathered data in the involved hospitals. Data on the mother's pregnancy, delivery, and newborn were collected from medical records by trained nurses. Parity, premature delivery, mode of delivery, APGAR scores at 5 min, and stillbirth were all included. The mothers who participated in the research filled out a self-administered questionnaire on their socioeconomic status, which included questions about their age, education level, employment status, and family income. Participants completed a self-administered questionnaire including information on socioeconomic status, and for illiterate participants, a well-trained nurses were responsible about face-to-face completing of the questionnaire.

This study followed a mixed cohort design. We recruited participants at the time of delivery; all risk exposures were collected retrospectively from the medical records of our participants during the index pregnancy. All immediate outcomes were collected prospectively within the first two days of delivery until mothers' discharge from the hospitals. Details of the full methodology can be found in the cohort profile registration.^[10] The study was conducted according to the principles expressed in the Declaration of Helsinki.

For the current report, all women with documented hemoglobin levels by laboratory examination in the mid-trimester were included. We excluded women with anemia due to causes other than iron deficiency (e.g., hemoglobinopathies, folate deficiency, etc.)

Participants were grouped according to the WHO classification of anemia into nonanemic, mildly anemic, moderately anemic, and severely anemic. The groups were compared in relation to sociodemographic characteristics such as education level and working status. In addition, medical and obstetric history including body mass index (BMI), age, chronic diseases including diabetes mellitus, parity, antenatal care, and the use of iron supplements were reported. The effects of anemia were investigated on the following maternal and neonatal outcomes: maternal admission to intensive care unit (ICU), APGAR scores <5 and 7, PTB, LBW, admission to neonatal ICU, stillbirth rate, and congenital anomalies detected by mid-trimester ultrasound scan.

Patient and public involvement statement

Despite the participants in this research not being involved in the development of the research question, design, or implementation of the study, the need of the mothers and their children for interventions to reduce anemia has transpired from previous studies, which showed an association between anemia during pregnancy and the unfavorable effects on the newborns and mothers.

Definitions

The following definitions were considered for this study:

- Classification of anemia during pregnancy according to the WHO classification:^[11]
 - Nonanemia (≥ 11.0 g/100 ml)
 - Mild (10–10.9 g/100 ml)
 - Moderate (7.09–9.9 g/100 ml)
 - Severe (< 7.0 g/100 ml).
- Maternal pregnancy BMI was calculated from maternal weight at 28–30 weeks gestation and height:^[12,13]
 - Normal weight (≤ 28.4 kg/m²)
 - Overweight (28.5–32.9 kg/m²)
 - Obese (≥ 33 kg/m²).
- Definitions for PTB:
 - Gestational age criteria:
 - Moderate to late preterm (32 to < 37 weeks)
 - Very preterm (28 to < 32 weeks)
 - Extremely preterm (< 28 weeks).
- Birth weight criteria:
 - LBW: Birth weight < 2500 g.
- Booked for antenatal care: Having at least one antenatal visit during the indexed pregnancy at the delivery hospital.

Statistical analysis

As only 12 women were classified as severe anemia (< 7 g/100 ml), statistical comparison was conducted to compare three groups; women without anemia (hemoglobin levels = 11 g/100 ml or more), women with mild anemia (hemoglobin level = 10–10.9 g/100 ml), and women with moderate anemia (hemoglobin level < 10 g/100 ml). Percentages and mean \pm standard deviation deviation were used for descriptive statistics. Chi-Square test and analysis of variance were used to compare discrete and continuous variables, respectively. A $P < 0.05$ was considered statistically significant. Logistic regression analysis was conducted to assess the independent effect of anemia on pregnancy outcomes after adjustment of maternal age and parity. Marginal probability of neonatal and maternal outcomes according to different hemoglobin level was plotted with its 95% confidence intervals (CI). Statistical analyses of the data were done using SPSS V.26.0 statistical package (IBM SPSS) and STATA version 16.

Ethical considerations

Ethical approval for the main cohort study (RAHMA) was provided by the Institutional Review Board at all participating centers. The study was conducted according to the principles of the Helsinki Declaration. Informed written consent was obtained from each participant, and all data were collected anonymously.

Results

A total of 10,600 pregnant women participated in this study, of whom 3261 (30.76%) were anemic, of which 1729 (16.3%), 1520 (14.3%), and 12 (0.1%) had mild, moderate, and severe anemia, respectively. Due to the small proportion of women with severe anemia, they were analyzed with women with moderate anemia.

Table 1 summarizes the difference in sociodemographic characteristics between anemic and non-anemic women. The mean age was similar in the three groups; however, older women were less likely to have anemia when compared to women younger than 30 years (odds ratio [OR]=0.94, CI 0.91–0.94), and primiparous women had higher odds of developing anemia compared to multiparous women (OR = 1.01, CI 0.90–1.14). Women who were booked for antenatal care and those who reported taking iron supplements were less likely to be anemic, (OR = 0.93, CI: 0.82–1.06) and (OR = 0.92, CI: 0.77–1.09), respectively.

Maternal and perinatal outcomes were compared in Table 2. Women with moderate anemia had increased odds for admission to ICU (OR = 1.60, CI 0.78–3.28). Compared to nonanemic women, those with moderate anemia were more likely to have PTB: Before 37 weeks: OR = 1.14 (CI: 0.96–1.37), before 34 weeks: OR = 1.10 (CI: 0.81–1.50), and before 32 weeks: OR = 1.14 (CI 0.77–1.71). Furthermore, women with moderate anemia had higher odds of delivering low-birth weight infants (OR = 1.04, CI: 0.87–1.23) and stillbirth (OR = 1.16, CI 0.72–1.85) as compared to nonanemic women. In addition, APGAR scores were significantly lower in women with moderate anemia compared to nonanemic women with an increased associated risk of APGAR < 7 (OR = 1.55, CI: 1.09–2.20) and APGAR < 5 (OR = 1.55, CI: 1.09–2.20). However, all tested associations did not reach statistical significance except APGAR scores association ($P < 0.05$).

To investigate the effect of anemia on the pregnancy outcomes, regression analyses were conducted to extrapolate the predicted probability (PP) using the marginal prediction.

Regression analysis confirmed the significant increase in the likelihood of low APGAR scores with the decrease in maternal hemoglobin level. An increment of maternal hemoglobin by 1 g/100 ml decreases the odds of low

Table 1: Association of anemia with participants' demographic and clinical characteristics (n=10,600)

	No anemia (11 or more) (n=7339; 69.2%), n (%)	Mild anemia (10-10.9) (n=1729; 16.3%), n (%)	Moderate anemia (<10) (n=1532; 14.5%), n (%)	P	OR (CI)
Age (mean±SD)	30.2±5.9	29.9±5.9	29.9±5.9	0.13	0.99 (0.98-1.00)
<30	3535 (68.4)	870 (16.8)	763 (14.8)		1
30-34	1970 (69.8)	432 (15.3)	421 (14.9)		0.94 (0.85-1.04)
35-39	1311 (70.5)	305 (16.5)	243 (13.1)		0.91 (0.83-1.02)
40+	498 (69.7)	117 (16.4)	99 (13.9)		0.94 (0.79-1.11)
Missing (36)					
Education				0.43	1.01 (0.75-1.37)
Illiterate	148 (68.8)	32 (14.9)	35 (16.3)		0.92 (0.83-1.03)
School	2542 (70.7)	584 (16.2)	468 (13.0)		1
University or above	1701 (69.1)	411 (16.7)	351 (14.3)		
Missing (4328)					
Occupation				0.61	0.96 (0.84-1.09)
Housewife	5693 (70.3)	1281 (15.8)	1127 (13.9)		1
Employee/student	815 (69.4)	184 (15.7)	176 (15.0)		
Missing (1324)					
BMI (kg/m ²)	31.7±5.7	31.8±5.8	31.9±5.9	0.42	
Normal	1999 (70.4)	442 (15.6)	400 (14.1)	0.73	1
Overweight	1982 (69.4)	474 (16.6)	398 (13.9)		1.05 (0.93-1.17)
Obese	2530 (69.9)	562 (15.5)	526 (14.5)		1.02 (0.92-1.14)
Missing (1287)					
Parity	3.8±2.6	3.7±2.6	3.8±2.7	0.69	
Primiparous	1486 (68.5)	368 (17.0)	316 (14.6)	0.88	1.01 (0.90-1.11)
Multiparous	3503 (69.2)	825 (16.3)	733 (14.5)		1
Grand multiparous (5+)	2337 (69.7)	533 (15.9)	483 (14.4)		0.89 (0.79-1.0)
Missing (16)					
Antenatal care				0.46	0.93 (0.82-1.06)
Booked for antenatal care	6521 (69.4)	1521 (16.2)	1355 (13.5)		0.92 (0.77-1.09)
Iron supplements	5820 (70.2)	1324 (16.0)	1146 (13.8)	0.48	
Comorbidities				0.65	1.11 (0.78-1.59)
Hypertension	93 (66.9)	22 (15.2)	24 (17.3)		0.99
Diabetes	221 (68.6)	52 (16.1)	49 (15.2)		1.04 (0.82-1.32)

OR=Odds ratio; CI=Confidence interval; BMI=Body mass index; SD=Standard deviation

APGAR (<7) by 9% (OR = 0.91, CI: 0.83–0.99). In addition, the PP of APGAR <7 progressively improved with the increase of maternal hemoglobin level, as it was 3% (CI: 2%–4%) when maternal hemoglobin level was 7 g/100 ml and attenuated to 1% (CI: 0.9%–2%) at maternal hemoglobin of 15 g/100 ml [Figure 1a]. In addition, the PP of PTB decreased as the level of maternal hemoglobin increased reaching its lowest value when the maternal hemoglobin level is 15 g/100 ml when the expected prevalence of PTB is 6.5% (CI: 5%–8%) [Figure 1b]. Similarly, the PP of LBW was the highest among women whose hemoglobin was 7 g/100 ml with expected prevalence of 12% (CI: 10%–13%) and decreased gradually reaching its lowest when maternal hemoglobin is 15 g/100 ml where the expected prevalence equals 11% (CI: 9%–12%) [Figure 1c]. The probability of having stillbirth dropped from 1.3% (CI: 0.7%–2.1%) among women with 7 g/100 ml hemoglobin level to 1.1% (CI: 0.7%–1.6%) among women whose hemoglobin level was 15 g/100 ml [Figure 1d]. The PP of maternal admission to ICU decreased from 0.8% (CI: 0.2%–1.5%) at

hemoglobin level of 7 g/100 ml to 0.2% (CI: 0.06%–0.4%) when hemoglobin level is 15 g/100 ml [Figure 1e].

Discussion

The results of this study showed that one-third of Saudi pregnant women in Riyadh had mild or moderate anemia during pregnancy, but very low prevalence of severe anemia. It also showed that parity other than primiparity, regular antenatal care, and iron supplementation are associated with a low risk of anemia during pregnancy. The odds of developing adverse effects of anemia during pregnancy did not reach statistical significance in this study, most probably due to the low prevalence of severe anemia compared to the majority of nonanemic women. Nevertheless, the PP from the data showed that anemia is associated with maternal admission to ICU, LBW, PTB, low APGAR scores, and stillbirth.

The prevalence of 30% for mild and moderate anemia in pregnancy reported in this cohort is relatively

Table 2: Maternal and perinatal outcomes of the study participants

Characteristic	No anemia (11 or more) (n=7339; 69.2%), n (%)	Mild anemia (10-10.9) (n=1729; 16.3%), n (%)	Moderate anemia (<10) (n=1532; 14.5%), n (%)	P
Gestational age at delivery	38.6±2.3	38.5±2.4	38.5±2.4	
<37 weeks	698 (9.6)	182 (10.6)	165 (10.9)	0.19
OR (CI)	1	1.11 (0.93-1.31)	1.14 (0.96-1.37)	
<32 weeks	126 (1.7)	37 (2.2)	30 (2.0)	0.45
OR (CI)	1	1.25 (0.86-1.81)	1.14 (0.77-1.71)	
<34 weeks	222 (3.0)	69 (3.5)	51 (3.4)	0.57
OR (CI)	1	1.15 (0.86-1.54)	1.10 (0.81-1.50)	
Missing (171)				
Maternal admission to ICU	30 (0.4)	4 (0.2)	10 (0.7)	0.17
OR (CI)	1	0.56 (0.20-1.60)	1.60 (0.78-3.28)	
Birth weight	3.1±0.56	3.1±0.57	3.1±0.57	0.85
Low birth weight	797 (10.9)	205 (11.9)	172 (11.3)	0.50
OR (CI)	1	1.10 (0.94-1.30)	1.04 (0.87-1.23)	
Missing (67)				
Intra uterine growth restriction	72 (1.0)	21 (1.2)	14 (0.9)	0.62
OR (CI)	1	1.24 (0.76-2.03)	0.93 (0.52-1.65)	
Missing (72)				
Congenital anomalies	105 (1.4)	24 (1.4)	20 (1.3)	0.93
OR (CI)	1	0.97 (0.62-1.51)	0.91 (0.56-1.47)	
Stillbirth	91 (1.2)	20 (1.2)	22 (1.4)	0.76
OR (CI)	1	0.93 (0.57-1.51)	1.16 (0.72-1.85)	
Missing (11)				
APGAR	8.9±1.0	8.9±1.1	8.7±1.2	<0.01
<7	131 (1.8)	35 (2.0)	42 (2.8)	0.05
<5	76 (1.0)	18 (1.1)	28 (1.8)	0.03
OR (CI)	1	1.14 (0.78-1.66)	1.55 (1.09-2.20)*	
NICU	315 (4.3)	79 (4.6)	75 (5.0)	0.58
OR (CI)	1	1.06 (0.83-1.37)	1.14 (0.88-1.48)	

NICU=Neonatal intensive care unit; low birth weight=(<2500 g); OR=Odds ratio; CI=Confidence interval; ICU=Intensive care unit; APGAR=Appearance, pulse, grimace, activity, and respiration; *P-value =0.03

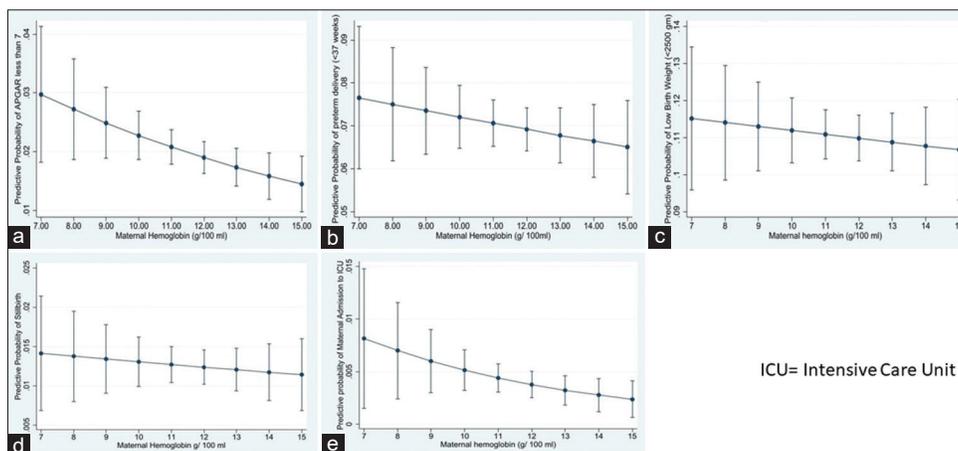


Figure 1: Predictive probability of pregnancy outcomes according to different maternal hemoglobin levels (a) APGAR <7, (b) Preterm delivery <37, (c) Low birth weight <2500 g, (d) stillbirth and (e) Maternal admission to intensive care unit

higher than the prevalence of 12%–22% reported in other high-income countries.^[2] This observation may be explained by the high prevalence of obesity reported in this cohort and the known association of obesity with high levels of hepcidin and its effect on the dysregulation of iron metabolism.^[14] Nevertheless, this is less than the

53% prevalence reported for South East Asia (SEA). Furthermore, the prevalence of severe anemia of 0.1% in this study is far less than the prevalence of 3.8% reported in SEA, especially if the population density is considered.^[15] Our finding of prevalence of 0.1% of severe anemia in this cohort is consistent with that of

0.4 (CI: 0.1–0.8) reported for the Middle East as a part of the global estimate of anemia by Stevens *et al.*^[12]

In contradistinction to the cohort in this study, low socioeconomic conditions and the associated risk factors highlight the demographic profile of women with anemia in many low- and middle-income communities.^[16] Modest education attainment, poor nutrition, limited access to antenatal care and micronutrient supplements (including iron), and multiparity with short periods of time between pregnancies are all known risk factors associated with anemia during pregnancy.^[17,18] Such factors hardly influence maternal anemia prevalence in our cohort due to the high economic status of the community.

Nearly 90% of the participants attended antenatal care, and over 90% took iron supplements during pregnancy; the protective effects of iron supplementation are noted in this cohort, which agrees with reports of previous studies.^[19] Regular iron supplementation during pregnancy for the prevention of anemia is recommended by the WHO based on the evidence that it reduces the risk of anemia by 50% and increases maternal hemoglobin by 3–5 g/100 ml.^[20] In addition, it is proven that, for each 1 g/100 ml increase in hemoglobin, maternal mortality is reduced by 20%.^[19]

The prediction models from the data of this study agree with the findings of previous studies about the association between severe IDA and adverse pregnancy outcomes. Lone *et al.* reported that anemia increases preterm delivery risk by four-fold, low APGAR scores risk by nearly two-fold, risk of stillbirth by four-fold, and LBW risk by almost two-fold.^[5] These results are consistent with effects of anemia on pregnancy outcomes with our predicted findings and the findings of other reports.^[21,22]

It is conceivable to consider fetal adverse outcomes as a spectrum of one syndrome of growth and development abnormality due to fetal hypoxia from the reduced maternal oxygen-carrying capacity resulting from anemia. Similar spectrum of fetal adverse outcomes with increase amniotic fluid erythropoietin has been reported in conditions associated with reduced oxygen-carrying capacity in the fetus.^[23]

Other reported adverse outcomes of severe IDA include postpartum hemorrhage, maternal death, and other near miss maternal morbidities.^[21,24,25] Those adverse outcomes could be consistent with our prediction of increased risk of maternal admission to ICU. However, maternal and fetal complications are mostly associated with severe anemia (hemoglobin \leq 7 g/100 ml) and vary with timing of anemia in relation to the trimester of pregnancy.^[26]

Our prediction models showed that PTB, LBW, and stillbirth reached lowest rates when maternal hemoglobin level was \geq 15 g/100 ml, which is consistent with a

recent finding from a systematic review that hemoglobin levels \geq 14 g/100 ml decreases the risk of PTB.^[26]

Implication to practice

The implementation and continuous evaluation of national health policy for surveillance of antenatal care investigations – including investigation of anemia – is an important intervention to be considered in modern Saudi Arabia. Such an undertaking coupled with universal iron supplementation, as recommended by the WHO, will improve maternal and infant health and well-being in the Kingdom. Health education targeted at pregnant women and those of reproductive age on the importance of micronutrients and iron supplementation is an important intervention to empower mothers and their families to have healthy pregnancies.

Implication to research

Data about the prevalence, causes, and effects of anemia in pregnancy in different parts of the Kingdom are scarce and outdated. Further research with accurate data is needed as a source for national health policy.

Strength and limitations

Our study included a large number of mothers from the Riyadh area in Saudi Arabia and reflected an accurate baseline estimate for the prevalence of anemia in pregnancy. In addition to that, it addresses the gap in information about an important public health problem, especially since the previous studies were outdated,^[8,27] or included a small number of participants;^[28,29] it can help in planning national health policies for investigation, prevention and treatment of anemia during pregnancy. The predictive models in this study provided valuable information about hemoglobin levels in relation to maternal and perinatal outcomes.

We are aware about some limitations of this study are due to the observational nature of the investigation and having missing data at each variable level; however, missing data for all variables are far below 20% except for the maternal education, yet there are good numbers in each category to maintain the power of the study and to insure the validity of regression analysis. Furthermore, the limitation of the diagnosis of anemia according to the hemoglobin levels in this study may have underestimated the prevalence of anemia. However, other tests such as serum ferritin, which was traditionally considered to give more accurate estimates of iron status during pregnancy,^[30] were proven to have modest diagnostic accuracy based on reports from recent studies.^[31]

Conclusion

More than a third of the pregnant women in Riyadh had mild to moderate anemia. The risk of anemia increased

in primipara, younger women, and those who did not attend antenatal care or take iron supplements. Predictive probability showed that anemia is associated with low APGAR scores, LBW, PTB stillbirth, and maternal admission to ICU.

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Conflicts of interest

There are no conflicts of interest.

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