

## The association between high hemoglobin levels and pregnancy complications, gestational diabetes and hypertension

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### ABSTRACT

Gestational diabetes mellitus (GDM) and hypertensive disorders of pregnancy (HDP) are the principal causes of maternal morbidity and mortality. The maternal morbidity and mortality burden for women is relatively high, suggesting a substandard quality of care. Therefore, an early diagnosis of GDM and gestational hypertension (GH) can improve prenatal care for pregnant women and improve pregnancy outcomes. Previous studies demonstrated that elevated Hb levels in the first trimester indicate possible pregnancy complications and should not only be considered as good iron status. However, ethnic differences could play a role in determining the magnitude of the association. We hypothesized that high Hb levels ( $\geq 12.5$  g/dl) in the first trimester (6-13 gestational weeks, GW) are associated with an increased risk of fasting blood sugar (FBS)  $\geq 126$  mg/dl, systolic blood pressure (SBP)  $\geq 140$  mmHg, and diastolic blood pressure (DBP)  $\geq 90$  mmHg among pregnant women visiting prenatal clinics.

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## Yuqori gemoglobin darajasi va homiladorlik asoratlari, homiladorlik diabeti va gipertenziya o'rtasidagi bog'liqlik

### ANNOTATSIYA

#### Kalit so'zlar:

onalar o'limi, onalar  
kasallanishi, ochlik qon

Homiladorlik qandli diabet (GDM) va homiladorlikning gipertonik kasalliklari (HDP) onalar kasallanishi va o'limining asosiy sabablari hisoblanadi. Ayollar uchun onalar kasallanishi

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shakar, yuqori gemoglobin darajasi, homiladorlik gipertenziyasi, homiladorlik qandli diabet.

va o'lim darajasi nisbatan yuqori, bu esa tibbiy xizmat sifatining pastligidan dalolat beradi. Shuning uchun, GDM va homiladorlik gipertenziyasi (GH) ning erta tashxisi homilador ayollarga prenatal yordamni yaxshilash va homiladorlik natijalarini yaxshilash mumkin. Oldingi tadqiqotlar shuni ko'rsatdiki, birinchi trimestrda Hb darajasining oshishi homiladorlikning mumkin bo'lgan asoratlarini ko'rsatadi va nafaqat yaxshi temir holati deb hisoblanishi kerak. Biroq, etnik tafovutlar uyushmaning hajmini aniqlashda rol o'ynashi mumkin. Birinchi trimestrdagi yuqori Hb darajalari ( $\geq 12,5$  g / dl) (6-13 homiladorlik haftasi, Gvt) ochlikdagi qon shakarining (FBS)  $\geq 126$  mg / dl, sistolik qon bosimi (SBP) xavfini oshirishi bilan bog'liq deb taxmin qildik. Prenatal klinikalarga tashrif buyurgan homilador ayollar orasida  $\geq 140$  mmHg va diastolik qon bosimi (DBP)  $\geq 90$  mmHg

## **Связь между высоким уровнем гемоглобина и осложнениями беременности, гестационным диабетом и артериальной гипертензией**

### **Ключевые слова:**

материнская смертность, материнская заболеваемость, уровень сахара в крови натощак, высокий уровень гемоглобина, гестационная гипертензия, гестационный диабет.

### **АННОТАЦИЯ**

Гестационный сахарный диабет (ГСД) и гипертензивные расстройства беременности (ГБН) являются основными причинами материнской заболеваемости и смертности. Бремя материнской заболеваемости и смертности среди женщин относительно велико, что свидетельствует о низком качестве медицинской помощи. Таким образом, ранняя диагностика ГСД и гестационной гипертензии (ГГ) может улучшить дородовой уход за беременными женщинами и улучшить исходы беременности. Предыдущие исследования показали, что повышенный уровень гемоглобина в первом триместре указывает на возможные осложнения беременности и не должен рассматриваться только как хороший статус железа. Однако этнические различия могут играть роль в определении величины ассоциации. Мы предположили, что высокие уровни Hb ( $\geq 12,5$  г/дл) в первом триместре (6-13 недель гестации, ГВ) связаны с повышенным риском повышения уровня сахара в крови натощак (FBS)  $\geq 126$  мг/дл, систолического артериального давления (САД)  $\geq 140$  мм рт.ст. и диастолическое артериальное давление (ДАД)  $\geq 90$  мм рт.ст. у беременных, посещающих женские консультации.

### **Introduction**

Gestational diabetes mellitus (GDM) and gestational hypertension (GH) significantly contribute to maternal, fetal, and neonatal morbidity and mortality [1]. The prevalence of GDM is rising worldwide and ranges from 1% to 20% [2]. During

normal pregnancy, progressive insulin resistance develops during mid-pregnancy and progresses through the third trimester [3]. Globally, hypertensive disorders of pregnancy (HDP) are one of the leading causes of peripartum morbidity and mortality [4]. HDP complicates up to 2.73% of all pregnancies and is responsible for 10-15% of all maternal mortality [5]. It is associated with a spectrum of severity, ranging from mild pregnancy-induced hypertension to eclampsia [5]. Moreover, it is among the most significant and intriguing problems in obstetrics [5]. Women are at higher risk of pregnancy complications due to the stressful life they live [6,7]. The burden of maternal morbidity and mortality for women is relatively high, suggesting a problem of substandard quality of care [6,7]. Moreover, HDP is under-treated among women and is associated with an increased risk of cesarean section, preeclampsia (PE), antepartum hemorrhage, postpartum hemorrhage, and chronic hypertension [8]. Early diagnosis of GDM and GH can improve prenatal care for pregnant women during pregnancy and result in a satisfactory pregnancy outcome [1].

Hemoglobin (Hb) measurement is a routine standard test for evaluating physical status among pregnant women on their first visit to primary health care clinics [9]. Throughout normal pregnancy, blood volume expands by an average of 50% compared with the non-pregnant state [10]. This rapid expansion of blood volume starts in the first trimester of pregnancy [11]. Moreover, plasma volume increases more than the increase in red blood cell (RBC) mass, which produces a net decline in hemoglobin concentration during the first half of pregnancy. This is known as the physiologic anemia of pregnancy [11]. Hb concentration reaches the nadir in the second trimester of pregnancy because a concurrent increase does not match the increase in plasma volume in RBC mass increase [12]. Based on the World Health Organization (WHO), anemia in pregnancy has different cutoffs based on the trimester (first trimester: <11.0 g/dl; second trimester: <10.5 g/dl; and third trimester: <11 g/dl) [13] while normal values are assigned from 11 to <12.5 g/dl [14]. Physicians and health care providers give more attention to maternal anemia than high blood levels. Previous studies demonstrated that elevated Hb levels in the first trimester indicate possible pregnancy complications and should not be mistaken for good iron status [15-22]. They also indicated that Hb levels during early pregnancy play a role in predicting the risk of GDM and PE [16-19]. Studies which investigated the association between high maternal Hb levels and adverse pregnancy outcomes are scarce and controversial, with no absolute cut-off values for high Hb levels [15-22]. The cutoffs used to define low or high hemoglobin concentrations in these studies differed considerably, which may have affected the likelihood of detecting relations with the outcomes [21]. Most often, only the most extreme cutoffs were significantly associated with pregnancy complications.

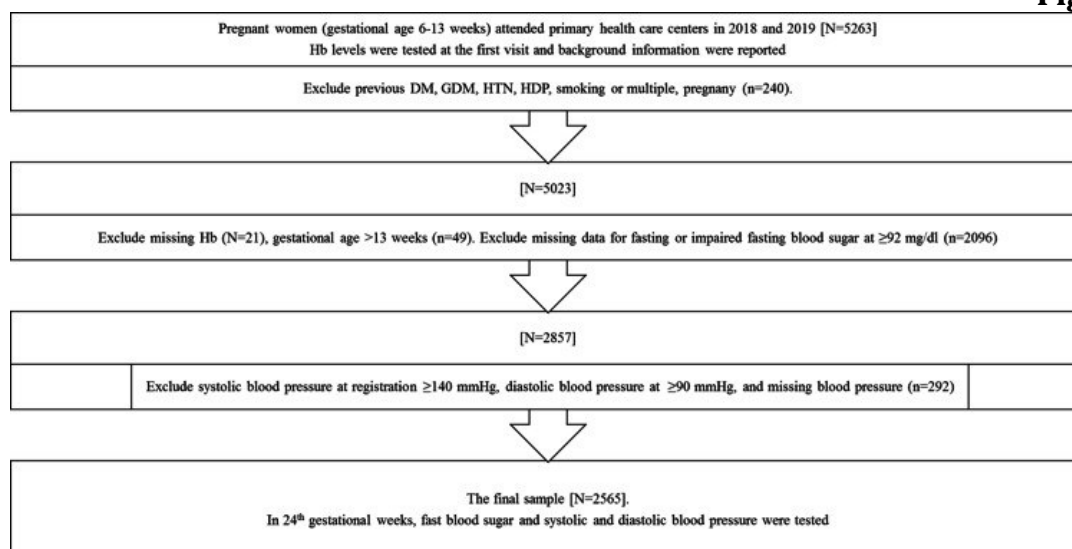
Further research is necessary to study and better understand the heterogeneity in the suggested cutoffs and risk factors associated with pregnancy outcomes. Moreover, it was suggested that ethnic differences could play a role in determining the magnitude of the association between high Hb and pregnancy complications [16]. Therefore, further investigation in different ethnicities was recommended. Based on the literature review, the assessment of high hemoglobin levels by which cutoff should be taken as standard is still not clear. Taking into consideration the limitations of these studies, the existing literature is insufficient. The adverse effects of high Hb at registration among

pregnant women have not been previously investigated. Therefore, we conducted a retrospective study to investigate the association between maternal Hb levels in the first trimester (6-13 gestational weeks, GW) and adverse pregnancy outcomes (i.e., gestational hypertension and diabetes) among pregnant women. We hypothesized that high Hb levels ( $\geq 12.5$  g/dl) in the first trimester (6-13 GW) are associated with an increased risk of fasting blood sugar (FBS)  $\geq 126$  mg/dl, systolic blood pressure (SBP)  $\geq 140$  mmHg, and diastolic blood pressure (DBP)  $\geq 90$  mmHg among pregnant women visiting prenatal clinics from January 2018 to December 2019. The results of this study could have important clinical implications for early screening, and improving preventive and curative health services to promote healthy pregnant women.

### Materials and methods

A cross-sectional study was performed in 2021 at primary healthcare centers. Low Hb levels were defined according to WHO and CDC definition (Hb  $< 11.0$  g/dl) [13] while normal Hb was defined as Hb ranging between 11.0 and 12.49 g/dl and high Hb concentration  $\geq 12.5$  g/dl [14]. Based on WHO definition, fasting plasma glucose during pregnancy  $\geq 92$  to  $< 126$  mg/dl (gestational diabetes) or fasting plasma glucose  $\geq 126$  mg/dl (diabetes mellitus) [23]. Other high biochemical and medical levels were defined as the following: high systolic blood pressure  $\geq 140$  mmHg, and high diastolic blood pressure  $\geq 90$  mmHg. All medical records (N=5263) were reviewed for pregnant women who attended primary healthcare centers of the MoH in these governorates in the years 2018 and 2019. The year 2020 was excluded from the study due to the COVID-19 pandemic and quarantine. Out of 5263 records, 2698 medical records were excluded from this study as they met the exclusion criteria. Women were excluded if they had a history of a current or previous diabetes mellitus (DM), GDM, abnormal FBS, hypertension, GH, HDP, multi-pregnancies, and smoking during pregnancy. This includes women who had: FBS  $\geq 92$  mg/dl or missing values for FBS (N=2096), blood systolic blood pressure  $\geq 140$ , diastolic blood pressure  $\geq 90$ , or missing values for blood pressure (N=292), missing hemoglobin values (N=21), ultrasound-based gestational age more than 13 weeks (N=49), or who were previously diagnosed with DM/GDM/hypertension/gestational hypertension, or taking drugs for these conditions (N=240; Figure Figure11).

**Figure 1**



## Results

A total of (N=5263) medical records for pregnant women were collected, and 2698 records were excluded. The final number of eligible records was 2565. At registration, the mean values for maternal age were  $26.9 \pm 5.8$  years, ultrasound-based gestational age ( $8.18 \pm 2.34$  weeks), Hb level ( $11.87 \pm 1.17$  g/dl), FBS ( $79.7 \pm 8.60$  mg/dl), systolic blood pressure ( $110.31 \pm 11.22$  mmHg), and diastolic blood pressure ( $70.6 \pm 9.52$  mmHg). At registration, 32.4% of the women had high Hb levels, 47.0% had normal Hb levels, and 20.5% had low Hb levels. At 24 GW, 32.4% of the women had high Hb levels, 45.5% had normal Hb levels, and 22.1% had low Hb levels. The percentage of high FBS ( $\geq 126$  mg/dl) at 24 GW was 4.4% and FBS (92 to  $< 126$  mg/dl) was 37.7% while 58.2% had normal FBS ( $< 92$  mg/dl). As previously mentioned, women who had FBS  $\geq 92$  mg/dl or systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg either at registration or before that were excluded from this study.

## Discussion

Management of pregnancy complications includes identifying and early management of these complications and identifying high-risk patients. This study aimed to investigate the association between high Hb levels at maternity care registration and various adverse health outcomes later in pregnancy (GDM and high blood pressure) among women attending primary care centers. In agreement with previous studies, our results indicated that women who had high Hb ( $\geq 12.5$  g/dl) at registration were at higher risk to have high FBS ( $\geq 126$  mg/dl) at 24 GW (OR 3.39, p-value  $< 0.001$ ) [16]. This association suggests that having a high Hb at registration in the first trimester increases the risk of developing GDM later in pregnancy. The reason for choosing 24 GW as a cutoff is that pregnant women at primary care centers get screened for GDM at that gestational age, which is consistent with the international recommendations [24]. These results could contribute to detecting high-risk pregnancies at registration in the first trimester among women, therefore prompting more intensive GDM risk factors modification and closer follow-ups than those with normal Hb levels. Moreover, the biochemical basis of this association is probably due to the effect of iron on decreasing insulin sensitivity by altering the expression of insulin receptors in hepatocytes [25]. Further research exploring the impact of high Hb in the first trimester on GDM will help better understand the etiology and pathophysiology of GDM. This will ultimately lead to decreasing the consequences of GDM, including high birth weight, shoulder dystocia, birth injuries, neonatal hypoglycemia, and jaundice [26]. Moreover, pregnant women with high Hb in the first trimester are three times more likely (OR=3.048) to have an increased risk of having high systolic blood pressure ( $\geq 140$  mmHg) at 24 GW (p-value=0.014) but not high diastolic blood pressure (p-value  $> 0.05$ ). This association between high Hb at registration in the first trimester and increased risk of gestational hypertension is consistent with a previous meta-analysis study [27]. However, that study confirms the association without specifying the type of HDP (systolic/diastolic/mixed) [27]. Hypertensive disorders in pregnancy remain the leading cause of maternal mortality worldwide [5]. Previous studies showed that high Hb levels during pregnancy result from hypovolemia or hemoconcentration, which is usually the result of PE or pregnancy-induced hypertension [10, 11]. An obvious mechanism for blood pressure increase with increased Hb levels would be a result of the increased blood viscosity. It

has been reported that the elevation of hematocrit and Hb levels increases blood viscosity and that increased viscosity through an effect on blood pressure may partly worsen cardiovascular function [28].

### Conclusions

Women who have a high hemoglobin level in their first trimester are at a higher risk of developing GDM and hypertension. Our findings suggest that the Hb level at registration could be utilized in predicting the risk of GDM and HDP among women who never had a previous history of these conditions. This early detection of high-risk pregnancies could lead to more intensive follow-ups or interventions, ultimately leading to decreased incidence and the adverse consequences of these conditions on pregnant women. We recommend considering high Hb at registration among women as a risk factor for having GDM and HDP later in pregnancy. Moreover, we recommend conducting further research investigating the difference in adverse pregnancy conditions prognosis (GDM and HDP) when considering high Hb at registration as a risk factor compared to currently considered risk factors. Furthermore, since Hb measurements are an inexpensive and widely available test, we recommend conducting further research on the association between high maternal Hb and other adverse outcomes and fetal complications among women. Further research is warranted about the exact pathophysiology of high Hb-induced isolated systolic hypertension and diabetes in pregnancy

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