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Severe anemia, sickle cell disease, and thalassemia as risk factors for hypertensive disorders in pregnancy in developing countries

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ABSTRACT

Objective: Hypertensive disorders during pregnancy are one of main causes for maternal and perinatal morbidity and mortality in developing countries. This study is to determine whether specific types of anemia are risk factors for hypertensive disorders during pregnancy in developing countries.

Methods: Using data from the World Health Organization Global Survey for Maternal and Perinatal Health, collected in hospitals in six African and six Latin American countries from 2007 to 2008 and in four Asian countries from 2004 to 2005, we examined the associations between severe anemia, sickle cell disease and thalassemia, and gestational hypertension or preeclampsia/eclampsia.

Results: A total of 214,067, 112,531, and 9,325 women were included in the analyses on severe anemia, sickle cell disease, and thalassemia, respectively. Multiparous women with severe anemia were at an increased risk of gestational hypertension (adjusted odds ratio (aOR): 1.73; 95% confidence interval (CI): 1.25–2.39). Severe anemia had a significant association with preeclampsia/eclampsia for nulliparous (aOR: 3.74; 95% CI: 2.90–4.81) and multiparous (aOR: 3.45; 95% CI: 2.79–4.25) women. Sickle cell disease exhibited a significant association with gestational hypertension among nulliparous (aOR: 2.41; 95% CI: 1.42–4.10) and multiparous (aOR: 3.26; 95% CI: 2.32–4.58) women. No significant associations were found between sickle cell disease and preeclampsia/eclampsia, or between thalassemia and either gestational hypertension or preeclampsia/eclampsia.

Conclusions: Severe anemia appears to be a risk factor for preeclampsia/eclampsia, while sickle cell disease may be a risk factor for gestational hypertension among women seeking hospital care in developing countries.

1. Introduction

Preeclampsia/eclampsia is a major contributor to maternal and perinatal morbidity around the world and is of particular concern as a cause of mortality in developing countries [1]. It is a complication specific to pregnancy and involves the development of hypertension and proteinuria, along with other systemic disturbances, during the second half of pregnancy [2]. Understanding of the pathogenesis of preeclampsia has evolved considerably, but aspects remain a subject of significant discussion. It is well established that beginning in early pregnancy, the placenta requires an increased blood supply, which necessitates remodeling of the maternal spiral arteries by cytotrophoblasts [3]. This process is inhibited in some cases of preeclampsia, leading to abnormal placentation [3]. Genetic and immune mechanisms, an enhanced systemic inflammatory response, and nutritional, hormonal, and angiogenic factors have also been implicated in preeclampsia [4]. Abnormal placentation may lead to hypoxic conditions of the placenta, which may contribute to the development of preeclampsia.

Meanwhile, anemia is a common consequence of pregnancy. The etiology of pregnancy-associated anemia is physiological hemodilution where a large increase in intravascular volume is not accompanied by an equivalent increase in red blood cells [5]. Hypoxic conditions of greater severity than mild anemia may contribute to the abnormal

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development of the placenta.

Severe anemia and sickle cell disease have been linked to pregnancy complications. In particular, multiple studies indicate that women with sickle cell disease are at an increased risk for a variety of perinatal and antepartum complications, such as preterm labor, preterm delivery and intrauterine growth restriction [6]. The red blood cell sickling, characteristic of sickle cell disease, is associated with hypoxia, anemia, vaso-occlusion and infection [7], which may be related to the pathogenesis of the preeclampsia syndrome. Only few studies listed gestational hypertension as an important potential outcome among women with sickle cell disease [6]. Thalassemia, another disease in the hemoglobinopathy family that alters hemoglobin synthesis and is characterized by anemia [8], could likewise be a candidate for predisposing to preeclampsia or similar hypertensive disorders during pregnancy. Yet the possible connections between such disorders and either thalassemia or severe anemia have rarely been examined.

Our study is to assess the relationship between three conditions—severe anemia, sickle cell disease and thalassemia—and both gestational hypertension and preeclampsia/eclampsia. We aim to provide further insight into the etiologic mechanisms involved in pregnancy-related hypertensive disorders and suggest additional avenues for future research.

2. Material and methods

2.1. Data

We performed a secondary analysis on data from the World Health Organization Global Survey for Maternal and Perinatal Health (WHOGS). All relevant institutions approved the survey, while our analysis was exempted from an Institutional Review Board review at the Shanghai Jiao Tong University and the National Institutes of Health. The protocol and methods of the WHOGS are described in detail elsewhere [9,10]. Briefly, the countries in which the WHOGS collected data were randomly chosen as part of a multistage stratified sampling procedure. Data were collected from 2004 to 2005 in Latin America and Africa and from 2007 to 2008 in Asia. This was a facility-based survey and women were enrolled in the study at admission for delivery at participating hospitals during a fixed period. Each hospital had a different window of time for enrolling subjects based on the total number of expected deliveries in a year relative to the population size for that site. Trained medical staff collected all of the data by means of a medical record review performed within a day after delivery, while the women and/or infants were followed until discharge, death or the seventh day post-partum.

2.2 Study population

In order to bolster statistical stability, we used data only from those countries that yielded at least 15 women who had both the risk factor (type of anemia) and gestational hypertension/preeclampsia/eclampsia. We then excluded women with a multiple gestation, chronic hypertension, diabetes mellitus and/ or a positive diagnosis of HIV. Subjects with missing data for any of these exclusion criteria, for critical variable or for parity were also removed from the analysis. Given that the number of subjects with two or more types of anemia was small (Supplementary Tables 3–11), we excluded women with a diagnosis of sickle cell anemia or thalassemia in the severe anemia group. Likewise, women with a diagnosis of severe anemia or thalassemia were excluded in the sickle cell disease group and women with severe anemia or sickle cell anemia were excluded in the thalassemia group. Therefore, each anemia disease was mutual exclusive among the groups. These restrictions resulted in study samples of 214,067, 112,531 and 9,325 women for the severe anemia, sickle cell diseases and thalassemia analyses, respectively (Table 1). And detailed information about the country and total number of severe anemia and sickle cell disease groups is presented in Supplementary Table 1 and Supplementary Table 2.

Table 1
Study sample selection.

	Severe anemia group[†]	Sickle cell disease group[††]	Thalassemia group[†††]
Overall sample (N)	229,245	123,625	9,838
Exclusion criteria (N)			
Multiple gestation	2,940	1,548	92
Chronic hypertension	2,227	1,510	62
Diabetes mellitus	1,837	942	214
HIV +	2,094	1,744	116
Other type of anemia[*]	2,327	2,167	54
Missing data (N)			
Exclusion Criteria	3,534	2,970	0
Parity	829	695	1
Key variable[**]	575	87	0
Study Sample(N) [***]	214,067	112,531	9,325

[†] Data from Algeria, Argentina, Brazil, Congo, Cuba, Ecuador, India, Kenya, Mexico, Niger, Nigeria, Peru, the Philippines, Sri Lanka, Thailand, and Uganda.

[††] Data from Brazil, Cuba, Ecuador, Kenya, Mexico, Niger, Nigeria, Thailand, and Uganda.

[†††] Data from Thailand.

* Sickle cell anemia and thalassemia cases are omitted from the severe anemia group; severe anemia and thalassemia cases are omitted from the sickle cell anemia group; severe anemia and sickle cell anemia cases are omitted from the thalassemia group.

** Exposure or outcome variables missing.

*** Some cases are omitted from the study sample for more than one reason, i.e., on the basis of multiple exclusion criteria, both forms of missing data, or at least one exclusion criterion and at least one form of missing data.

According to the study protocol, severe anemia was defined as hemoglobin levels < 7 g/dl. Sickle cell disease and thalassemia were determined based on standard clinical care tests for the condition. A woman was classified, per protocol, as having gestational hypertension if (1) she exhibited high blood pressure—an overall reading of 140/90 mmHg or greater, recorded on at least two occasions six or more hours apart, (2) the elevated blood pressure was observed after 20 weeks gestation, and (3) she was previously normotensive. A woman was classified as having preeclampsia/eclampsia if she met the criteria for gestational hypertension and substantial proteinuria. Such women were then excluded from the gestational hypertension group.

2.3 Statistical analysis

We first compared the prevalence of severe anemia, sickle cell disease and thalassemia and the prevalence of both gestational hypertension and preeclampsia/eclampsia across the study participants with respect to major demographic characteristics (age, marital status, education), reproductive histories (gravidity, outcome of last pregnancy, birth weight of last infant delivered) and selected health factors (preexisting cardiac or renal conditions), further stratified by parity. Differences in prevalence between those affected and unaffected by one of the anemia risk factors were tested for significance using standard chi-square tests.

We also analyzed the relationships between the types of anemia and other risk factors and the occurrence of gestational hypertension and preeclampsia/eclampsia via the unadjusted and adjusted odds ratios (ORs), and their 95% confidence intervals (CIs), estimated by means of separate multivariate logistic regression models for nulliparous and multiparous women.

The reference groups consisted of those without any type of anemia in each group. Based on the frequency distributions of preeclampsia, we set the reference groups to be 20–24 years of age for nulliparous women and 25–29 years of age for multiparous women. Married/cohabitating