

Iron and Oxidative Status Following Routine Iron Supplementation: Reflection on Pregnancy Outcomes in a Cohort of Women in Kinshasa, DR Congo

Andy Mbangama Muela, Barthélémy Tandu-Umba*, Roger Mbungu Mwimba

Department of Obstetrics and Gynecology, University Clinics of Kinshasa, Kinshasa, Congo

Email: dymuela@yahoo.fr

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Abstract

Background: Anemia during pregnancy is associated with oxidative stress, which might expectedly provoke harmful consequences on maternal and perinatal outcomes. Use of iron in women during pregnancy improves maternal hematologic parameters, while likely to worsen oxidative status. **Objectives:** Our study thus aimed to assess adverse outcomes on all women having been routinely iron supplemented during pregnancy. **Methods:** This is a prospective observational cohort of 74 pregnant women with singleton pregnancy whose baseline iron and oxidative status along with variations throughout pregnancy have been recently assessed at university clinics of Kinshasa, DR Congo. Obstetrical adverse outcomes were assessed according to the diagnosis of anemia and oxidative stress considered at recruitment, at 28 - 32 weeks of gestation and at term. For statistical calculations, we used t-test, chi-square test, ANOVA and regression, the significance being stated at $p < 0.05$. **Results:** Complications significantly associated with anemia at the beginning of pregnancy were acute fetal distress (OR = 3.9, $p < 0.03$), prematurity (OR = 7.3, $p < 0.007$), low birth weight or LBW (OR = 3.4, $p < 0.05$), birth asphyxia (OR = 15.1, $p < 0.002$) and neonatal hypoglycemia (OR = 3, $p < 0.05$). When the diagnosis of anemia was considered at 28 - 32 weeks of gestation, significant associations were found with gestational diabetes mellitus or GDM (OR = 3.8, $p < 0.05$), cesarean section (OR = 4.8, $p < 0.003$), prematurity (OR = 5.3, $p < 0.03$), birth asphyxia (OR = 10.9, $p < 0.008$) and neonatal hypoglycemia (OR = 4.7, $p < 0.02$). At term, the diagnosis of anemia was significantly associated with GDM (OR = 9.2, $p < 0.01$), premature rupture of membranes or PROM (OR = 2.8, $p < 0.05$), cesarean section (OR = 6.03, $p < 0.01$), birth asphyxia (OR = 2.9, $p < 0.05$) and neonatal hypoglycemia (OR = 3, $p < 0.05$).

*We regret to announce the death of Professor Barthelemy Tandu-Umba since March 25, 2019.

As of oxidative stress diagnosed at recruitment, significant associations were found with PROM (OR = 9, $p < 0.02$), cesarean section (OR = 3.7, $p < 0.05$), prematurity (OR = 6.4, $p < 0.02$), birth asphyxia (OR = 13.2, $p < 0.004$) and neonatal hypoglycemia (OR = 2.6, $p < 0.05$). The diagnosis of oxidative stress at 28 - 32 weeks of gestation was found significantly associated with acute fetal distress (OR = 4.2, $p < 0.02$), cesarean section (OR = 2.9, $p < 0.05$), LBW (OR = 9.9, $p < 0.002$), birth asphyxia (OR = 3.9, $p < 0.05$) and neonatal hypoglycemia (OR = 3.2, $p < 0.04$). For oxidative stress diagnosed at term, significant associations concerned GDM (OR = 11.4, $p < 0.006$), preeclampsia or PE (OR = 4.3, $p < 0.03$), acute fetal distress (OR = 8.3, $p < 0.003$), cesarean section (OR = 4.3, $p < 0.007$), prematurity (OR = 6, $p < 0.02$), LBW (OR = 4.3, $p < 0.03$), birth asphyxia (OR = 12.4, $p < 0.005$) and neonatal hypoglycemia (OR = 3.5, $p < 0.04$). **Conclusion:** Outcomes found significantly associated with oxidative stress seem to overlap those linked to anemic condition. Similarity between complications of anemia and that of oxidative stress is more observed at 28 - 32 weeks of gestation. This strongly suggests that major correction in both anemic and oxidative status should be initiated long before this landmark.

Keywords

Routine Iron Supplementation, Iron and Oxidative Status, Pregnancy Outcomes, Kinshasa

1. Introduction

Maternal iron-deficiency anemia is well known to be associated with high risk of shortening of pregnancy, impairment of fetal growth in terms of low birth weight (LBW) [1] [2], as well as significant decreased Apgar score during the first and the fifth minute [3].

Use of iron in women during pregnancy improves hematologic values [4] [5] and is expected to prevent these adverse outcomes. The beneficial effect has been evidenced as depending on dose of iron, duration of use, and baseline hemoglobin (Hb) concentration before treatment [5] [6].

However, iron supplementation both reverses the weakening of anti-oxidant defenses and increases lipid peroxidation [5] [7]-[12], which has been claimed to increase the generation of free radicals leading to oxidative stress [13] [14] [15] [16].

Consequences associated with damages resulting from stress mediators cover a wide field of manifestations such as gestational diabetes mellitus (GDM), preeclampsia (PE), premature rupture of membranes (PROM) and fetal outcomes such as prematurity, LBW, macrosomia, perinatal morbidity/death, and postpartum infections [17]. So, anemic condition is likely to generate the same consequences as that attributed to pro-oxidant properties of iron used to prevent it [18].

Evolution of iron and related oxidative status alongside iron supplementation thus means that beneficial effect of the treatment will vary according to the level of iron-deficiency throughout pregnancy [5]. Therefore, a routine administration may be harmful for women who are or become iron-replete at any period of supplementation. Indeed, possibility of adverse outcomes, along with that of oxidative damage due to iron overload, has been found lower or higher if the diagnosis of anemia is considered at the beginning, mid-pregnancy or later during pregnancy.

The present study thus aimed to assess adverse pregnancy outcomes on all women having been routinely iron supplemented during pregnancy in order to answer the question: can iron supplementation prevent as well as induce maternal and perinatal complications of oxidative stress?

2. Methods

The current study is a prospective observational cohort of 74 pregnant women with singleton pregnancy and was approved by the Ethics Committee of the School of Public Health of the University of Kinshasa, DR Congo. It was conducted during 10 months (from September 2017 throughout June 2018), the protocol of which was recently published [19]. The study sample was represented by pregnant women with pregnancy not exceeding 19 weeks (starting point of iron supplementation), without obvious pathology likely to have a negative influence on pregnancy (hypertension, diabetes mellitus, sickle cell disease, HIV, malaria, respiratory insufficiency) and regardless of age and parity. Eligible women were definitely recruited after informed and written consent to participate in the study. Only women reaching fetal viability (28 weeks of gestation) were selected. Irrespective of their biochemical status, all women of this cohort received routine Fe supplementation according to the national policy. Women with anemia (hemoglobin or Hb < 10 g/dl) took iron tablets for curative purposes (320 mg/day of ferric ammonium citrate), while the others received preventive iron supplementation (160 mg/day of ferric ammonium citrate). Let us note that these dosages have never been questioned in the country. Iron was associated with 15 mg folate/day. Nutritional iron intake was measured through a 24-hour recall using a questionnaire of common foods, including stuffs and habits likely to impede iron absorption, such as pica/geophagia, tannins and fibers. Supplemental iron intake was determined with a sheet containing details on the duration of the treatment. Additionally to baseline measurements at recruitment (± 15 weeks of gestation) blood sampling and analysis were carried out at 28 - 32 weeks and at term [5] [20]. Biological parameters were: Hb, hematocrit, ferritin, serum iron, transferrin and iron saturation capacity for iron status and superoxide dismutase (SOD), uric acid, oxidized low-density lipoprotein (LDL) and fasting blood glucose for oxidative status.

Throughout confinement adverse obstetrical outcomes were registered in terms of preterm labor and premature delivery (<37 weeks of gestation), PE (hypertension considered as blood pressure $\geq 140/90$ mmHg), GDM (to be di-

agnosed between weeks 26 and 28 of gestation using a glucose tolerance test according to the “Hyperglycaemia and Adverse Pregnancy Outcomes or HAPO study” [21]), PROM, prematurity (birth between 28 weeks of gestation and 37 weeks), LBW (birth weight < 2500 g), stillbirth (defined as death of a fetus after 28 weeks of gestation), perinatal mortality (deaths including stillbirths and neonatal deaths before 7 days of life), birth asphyxia or neonatal distress (defined as an Apgar score < 7 at the fifth minute) and any other neonatal or postpartum morbidity [19].

Data were registered using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA, 2007) and after transfer to statistical package for social sciences or SPSS (version 18.0; SPSS Inc., Chicago, IL, USA). For statistical calculations, univariate analyses (odds ratios [ORs]) were stratified in a dichotomic way (with or without anemia, with and without oxidative stress, with and without iron/oxidative status variations) to seek significant association with adverse pregnancy outcomes. Multivariate calculations (regression) using various risk factors were aimed at isolating those significantly influencing occurrence of complications in anemic/stressed mothers. Results are given with 95% confidence intervals (CIs), and $p < 0.05$ was considered significant.

3. Results

Women of the study ($n = 74$) were recruited at 15.9 ± 1.7 weeks of gestation and were aged 32.2 ± 5.2 years. Anemia was diagnosed to 39 women that represented 52.2% of the study group. Their main characteristics were as follow: 69.2% of which from low socioeconomic level, mean parity, weight, and body mass index or BMI of 2 ± 1 , 70.2 ± 14.5 Kg and 26 ± 5.2 Kg/m², respectively. The proportion of intestinal parasitosis (48.6%) was significantly higher among anemic women (61.5% vs 34.3%; $P < 0.02$) that had significantly lower alimentary iron intake (22.8 ± 4.9 gr vs 31.4 ± 9.5 gr; $P < 0.001$). No stillbirth was observed.

Maternal and neonatal characteristics at delivery are depicted in **Table 1**. The mean gestational age was 37.5 ± 1.9 weeks and 81.1% of deliveries occurred at term and in 55.4% of cases by vaginal delivery. The mean of birth weight was 2978.9 ± 626.1 gr. Average Apgar score was 8 ± 1 at birth, 9 ± 1 at the fifth and 9 ± 1 at the tenth minute. **Table 1** show that 82.4% of newborns had a good Apgar score at birth, 95.9% at the fifth and all of them at the tenth minute. There were significantly more newborns with LBW (28.2% vs 11.4%, $p < 0.04$) and those with a bad Apgar at the 1st minute (25.6% vs 8.6%, $p < 0.04$) in the group of pregnant women with anemia.

Table 2 present adverse outcomes that were registered in the study sample, namely: GDM, PE, PROM, acute fetal distress, cesarean section, prematurity, LBW, birth asphyxia (neonatal distress) and neonatal hypoglycemia.

The adverse outcomes that were significantly more frequent in the group of pregnant women with anemia compared to those without anemia are (**Table 3** and **Table 4**):

- at the beginning of pregnancy (14 - 19 weeks): acute fetal distress (76.5% vs

23.5%, $p < 0.03$), prematurity (85.7% vs 14.3%, $p < 0.01$), LBW (75% vs 25, $p < 0.05$), birth asphyxia (92.3% vs 7.7%, $p < 0.01$) and neonatal hypoglycemia (72.2% vs 27.8%, $p < 0.05$);

- at the middle of pregnancy (28 - 32 weeks): GDM (81.3% vs 18.8%, $p < 0.05$), PROM (90% vs 10%, $p < 0.04$), caesarean section (78.8% vs 21.2%, $p < 0.01$), prematurity (85.7% vs 14.3%, $p < 0.03$), birth asphyxia (92.3% vs 7.7%, $p < 0.01$) and neonatal hypoglycemia (83.3% vs 16.7%, $p < 0.02$);
- and at the end of pregnancy: GDM (87.5% vs. 12.5%, $p < 0.01$), PE (75% vs. 25%, $p < 0.05$), caesarean section (75.8% vs 24.2%, $p < 0.001$) and neonatal hypoglycemia (72.2% vs 27.8%, $p < 0.05$).

Using non adjusted OR, the next step of our calculations (**Tables 5-7**) questioned the effect of anemia and oxidative stress on each of these outcomes.

Table 1. Maternal and neonatal characteristics at delivery.

Characteristics	Overall group	Anemic women (n = 39)	Non anemic women (n = 35)	P
Age (yrs)	32.2 ± 5.2	32.3 ± 4.7	32.03 ± 5.7	0.82
Parity	2 ± 1	2 ± 1	2 ± 1	0.171
Gravidity	3 ± 1	3 ± 1	3 ± 1	0.247
Gestational age at delivery				
Mean	37.5 ± 1.9 weeks	37.4 ± 1.9 weeks	37.6 ± 1.8 weeks	0.586
<37 weeks	14 (18.9%)	10 (25.6%)	4 (11.4%)	0.103
≥37 weeks	60 (81.1%)	29 (74.4%)	31 (88.6%)	
Mode of delivery				
Vaginal delivery	41 (55.4%)	19 (48.7%)	22 (62.9%)	0.162
Cesarean section	33 (44.6%)	20 (51.3%)	13 (37.1%)	
Birth weight				
Mean	2978.9 ± 626.1 gr	2860 ± 610.7 gr	3111.4 ± 624.9 gr	0.085
LBW (<2500 gr)	15 (20.3%)	11 (28.2%)	4 (11.4%)	
Normal birth weight (2500 - <4000 gr)	52 (70.3%)	26 (66.7%)	26 (74.3%)	<0.04
Macrosomia (≥4000 gr)	7 (9.5%)	2 (5.1%)	5 (14.3%)	
Apgar score at the first minute				
Mean	8 ± 1	7 ± 1	8 ± 1	<0.04
<7	13 (17.6%)	10 (25.6%)	3 (8.6%)	<0.05
≥7	61 (82.4%)	29 (74.4%)	32 (91.4%)	
Apgar score at the fifth minute				
Mean	9 ± 1	8 ± 1	9 ± 1	0.176
<7	3 (4.1%)	1 (2.6%)	2 (5.7%)	0.459
≥7	71 (95.9%)	38 (97.4%)	33 (94.3%)	
Apgar score at the tenth minute				
Mean	9 ± 1	9 ± 1	9 ± 1	<0.04
<7	-	-	-	-
≥7	74 (100%)	39 (100%)	35 (100%)	

Table 2. Adverse pregnancy outcomes of the study sample based on anemia (Hb < 10 g/dl).

Outcomes	14 - 19 weeks						28 - 32 weeks						At term				
	Total (n = 74)		Anemia (n = 39)		Normal (n = 35)		Anemia (n = 44)		Normal (n = 30)		Anemia (n = 39)		Normal (n = 35)		p		
GDM	16	21.6	8	50	8	50	0.514	13	81.2	3	18.8	<0.05	14	87.5	2	12.5	<0.01
PE	16	21.6	9	56.2	7	43.8	0.486	11	68.8	5	31.2	0.288	12	75	4	25	<0.05
PROM	10	13.5	7	70	3	30	0.202	9	90	1	10	<0.04	6	60	4	40	0.440
Acute fetal distress	17	23	13	76.5	4	23.5	<0.03	12	70.6	5	29.4	0.218	10	58.8	7	41.2	0.384
Cesarean section	33	44.6	20	60.6	13	39.4	0.162	26	78.8	7	21.2	<0.01	25	75.8	8	24.2	<0.001
Prematurity	14	18.9	12	85.7	2	14.3	<0.01	12	85.7	2	14.3	<0.03	10	71.4	4	28.6	0.103
LBW	16	21.6	12	75	4	25	<0.05	11	68.8	5	31.2	0.288	6	37.5	10	62.5	0.137
Birth asphyxia	13	17.6	12	92.3	1	7.7	<0.01	12	92.3	1	7.7	<0.01	8	61.5	5	38.5	0.348
Neonatal hypoglycemia	18	24.3	13	72.2	5	27.8	<0.05	15	83.3	3	16.7	<0.02	13	72.2	5	27.8	<0.05

Table 3. Adverse pregnancy outcomes of the study sample based on SOD (normal 785 - 1570 UI/L).

Outcomes	14 - 19 weeks					28 - 32 weeks					At term				
	Pathologic SOD (n = 60)		Normal SOD (n = 14)		p	Pathologic SOD (n = 52)		Normal SOD (n = 22)		p	Pathologic SOD (n = 48)		Normal SOD (n = 26)		p
GDM	14	87.5	2	12.5	0.368	13	81.2	3	18.8	0.222	15	93.8	1	6.2	<0.01
PE	13	81.2	3	18.8	0.647	12	75	4	25	0.447	11	68.8	5	31.2	0.478
PROM	8	80	2	20	0.607	5	50	5	50	0.129	7	70	3	30	0.507
Acute fetal distress	15	88.2	2	11.8	0.319	13	76.5	4	23.5	0.377	12	70.6	6	29.4	0.398
Cesarean section	30	90.9	3	9.1	<0.05	27	81.8	6	18.2	<0.05	27	81.8	6	18.2	<0.01
Prematurity	12	85.7	2	14.3	0.476	9	64.3	5	35.7	0.403	8	57.1	6	42.9	0.353
LBW	15	93.8	1	6.2	0.133	11	68.8	5	31.2	0.553	9	56.2	7	43.8	0.298
Birth asphyxia	12	92.3	1	7.7	0.237	9	69.2	4	30.8	0.584	8	61.5	5	38.5	0.509
Neonatal hypoglycemia	15	83.3	3	16.7	0.541	14	77.8	4	22.2	0.313	12	66.7	6	33.3	0.545

Table 4. Adverse pregnancy outcomes of the study sample based on oxidized LDL (normal < 600 UI/L).

Outcomes	14 - 19 weeks					28 - 32 weeks					At term				
	Pathologic oxidized LDL (n = 41)		Normal oxidized LDL (n = 33)		p	Pathologic oxidized LDL (n = 38)		Normal oxidized LDL (n = 36)		p	Pathologic oxidized LDL (n = 42)		Normal oxidized LDL (n = 32)		p
GDM	9	56.3	7	43.8	0.584	6	37.5	10	62.5	0.166	8	50	8	50	0.368
PE	8	50	8	50	0.416	11	68.8	5	31.3	0.098	13	81.2	3	18.8	<0.03
PROM	9	90	1	10	<0.02	3	30	7	70	0.133	7	70	3	30	0.290

Continued

Acute fetal distress	12	70.6	5	29.4	0.123	13	76.5	4	23.5	<0.02	15	88.2	2	11.8	<0.003
Cesarean section	20	60.6	13	39.4	0.284	18	54.5	15	45.5	0.398	21	63.6	12	36.4	0.202
Prematurity	12	85.7	2	14.3	<0.02	8	57.1	6	42.9	0.428	12	85.7	2	14.3	<0.02
LBW	10	62.5	6	37.5	0.362	14	87.5	2	12.5	<0.002	13	81.2	3	18.8	<0.03
Birth asphyxia	12	92.3	1	7.7	<0.01	10	76.9	3	23.1	<0.05	12	92.3	1	7.7	<0.004
Neonatal hypoglycemia	13	72.2	6	27.8	<0.05	13	72.2	5	27.8	<0.04	14	77.8	4	22.2	<0.04

Table 5. Adverse maternal and perinatal outcomes associated with anemia (<10 g/dl).

Outcomes	14 - 19 weeks			28 - 32 weeks			At term		
	p	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%
GDM	0.514	1.1	0.5 - 2.7	<0.05	3.8	1.1 - 14.7	<0.01	9.2	1.9 - 44.4
PE	0.486	1.2	0.4 - 3.7	0.288	1.7	0.5 - 5.4	<0.05	3.4	1.1 - 11.9
PROM	0.202	2.3	0.6 - 9.8	<0.04	7.5	1.9 - 62.4	0.440	1.4	0.4 - 5.5
Acute fetal distress	<0.03	3.9	1.1 - 13.3	0.218	1.9	0.6 - 6.02	0.384	1.4	0.5 - 4.1
Cesarean section	0.162	1.8	0.7 - 4.5	<0.003	4.8	1.7 - 13.4	<0.01	6.03	2.2 - 16.8
Prematurity	<0.007	7.3	1.5 - 35.6	<0.03	5.3	1.1 - 25.5	0.103	2.7	0.8 - 9.5
LBW	<0.05	3.4	1.1 - 11.9	0.288	1.7	0.5 - 5.4	0.137	1.9	0.8 - 4.6
Birth asphyxia	<0.002	15.1	1.9 - 123.6	<0.008	10.9	1.3 - 88.9	0.348	1.6	0.5 - 5.3
Neonatal hypoglycemia	<0.05	3	1.1 - 9.6	<0.02	4.7	1.2 - 17.9	<0.05	3	1.01 - 9.6

Table 6. Adverse outcomes associated with pathologic iron status.

Outcomes	FERRITIN (<15 ou >150 ng/mL)									Serum iron (>31 µg/dl)								
	14 - 19 weeks			28 - 32 weeks			At term			14 - 19 weeks			28 - 32 weeks			At term		
	p	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%
GDM	0.611	1	0.3 - 3.03	0.071	2.7	0.9 - 8.6	0.147	2.2	0.7 - 7.1	0.313	2.02	0.4 - 10.1	0.630	1.1	0.2 - 5.9	0.527	1.7	0.2 - 15.5
PE	0.199	1.9	0.6 - 5.9	0.591	1.03	0.3 - 3.1	0.317	1.6	0.5 - 4.8	0.186	1.8	0.7 - 4.4	0.630	1.1	0.2 - 5.9	0.473	1.4	0.4 - 4.8
PROM	<0.05	4.8	1.1 - 24.5	0.209	2.2	0.6 - 8.5	<0.05	2.8	1.1 - 9.8	0.674	1.02	0.2 - 5.4	0.594	1.5	0.2 - 13.1	0.655	1.1	0.2 - 7.2
Acute fetal distress	0.134	2.2	0.7 - 6.7	0.116	2.3	0.8 - 6.9	0.433	1.3	0.4 - 3.9	<0.005	3.5	1.6 - 7.5	0.414	1.4	0.5 - 3.9	0.194	2.1	0.8 - 5.4
Cesarean section	0.500	1.1	0.5 - 2.8	0.146	1.8	0.7 - 4.7	0.106	2.03	0.8 - 5.2	0.317	1.3	0.7 - 2.2	0.515	1.2	0.3 - 4.8	<0.03	2.1	1.4 - 3.2
Prematurity	<0.04	3.1	1.1 - 10.8	0.392	1.4	1.4 - 4.5	0.482	1.2	0.5 - 3.02	0.301	1.6	0.6 - 4.3	0.393	2.3	0.3 - 19.8	0.396	1.6	0.4 - 5.7
LBW	<0.03	3.9	1.1 - 13.8	0.368	1.4	0.5 - 4.3	0.147	2.2	0.7 - 7.1	<0.05	2.4	1.02 - 5.5	0.370	1.5	0.5 - 4.3	0.473	1.4	0.4 - 4.8
Birth asphyxia	<0.008	7.4	1.5 - 36.3	<0.04	3.7	1.03 - 13.5	0.388	1.5	0.4 - 4.9	<0.004	4.6	1.8 - 11.7	<0.05	2.8	1.1 - 7.5	<0.05	2.9	1.03 - 8.03
Neonatal hypoglycemia	<0.03	3.5	1.1 - 11.1	0.174	1.9	0.7 - 5.7	0.551	1.1	0.4 - 3.2	<0.04	2.5	1.2 - 5.4	0.542	1.3	0.3 - 6.9	0.222	1.9	0.7 - 5.02

Table 7. Adverse outcomes associated with oxidative stress.

Outcomes	SOD (<785 ou > 1570 UI/L)									Oxidized LDL (>600 UI/L)								
	14 - 19 weeks			28 - 32 weeks			At term			14 - 19 weeks			28 - 32 weeks			At term		
	p	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%
GDM	0.368	1.8	0.4 - 9.2	0.222	2.1	0.5 - 8.3	<0.006	11.4	1.4 - 91.9	0.584	1.1	0.3 - 3.2	0.166	1.8	0.7 - 4.3	0.368	1.3	0.6 - 3.1
PE	0.647	1.01	0.3 - 4.2	0.447	1.4	0.4 - 4.8	0.478	1.3	0.4 - 4.1	0.416	1.2	0.5 - 2.9	0.098	2.5	0.8 - 8.2	<0.03	4.3	1.1 - 16.8
PROM	0.607	1.1	0.3 - 4.5	0.129	2.4	0.8 - 7.4	0.507	1.3	0.3 - 5.6	<0.02	9	1.1 - 75.2	0.133	2.5	0.7 - 8.8	0.290	1.9	0.5 - 8.2
Acute fetal distress	0.319	2	0.4 - 9.9	0.377	1.5	0.4 - 5.3	0.398	1.5	0.4 - 4.5	0.123	2.3	0.7 - 7.4	<0.02	4.2	1.2 - 14.3	<0.003	8.3	1.7 - 39.8
Cesarean section	<0.05	3.7	1.1 - 14.5	<0.05	2.9	1.1 - 8.5	<0.007	4.3	1.5 - 12.6	0.284	1.5	0.6 - 3.7	0.398	1.3	0.5 - 3.2	0.202	1.7	0.7 - 4.3
Prematurity	0.476	1.5	0.3 - 7.6	0.403	1.3	0.5 - 3.5	0.353	1.4	0.5 - 3.6	<0.02	6.4	1.3 - 31.2	0.428	1.3	0.4 - 4.3	<0.02	6	1.2 - 29.1
LBW	0.133	4.3	0.5 - 35.9	0.553	1.1	0.4 - 2.7	0.298	1.4	0.6 - 3.4	0.362	1.5	0.5 - 4.5	<0.002	9.9	2.1 - 47.7	<0.03	4.3	1.1 - 16.8
Birth asphyxia	0.237	3.3	0.4 - 27.4	0.584	1.1	0.4 - 3.1	0.509	1.2	0.4 - 3.2	<0.004	13.2	1.6 - 108.2	<0.05	3.9	1.1 - 15.7	<0.005	12.4	1.5 - 101.4
Neonatal hypoglycemia	0.541	1.2	0.3 - 4.9	0.313	1.7	0.5 - 5.8	0.545	1.1	0.4 - 3.4	<0.05	2.6	1.01 - 8.3	<0.04	3.2	1.01 - 10.3	<0.04	3.5	1.03 - 11.9

Complications significantly associated with anemia at the beginning of pregnancy were acute fetal distress (OR = 3.9; CI 95%: 1.1 - 13.3; $p < 0.03$; OR = 3.5; CI 95%: 1.6 - 7.5; $p < 0.005$ based on serum iron), prematurity (OR = 7.3; CI 95%: 1.5 - 35.6; $p < 0.007$; OR = 3.1; CI 95%: 1.1 - 10.8; $p < 0.04$ based on ferritin), LBW (OR = 3.4; CI 95%: 1.1 - 11.9; $p < 0.05$; OR = 3.9; CI 95%: 1.1 - 13.8; $p < 0.03$ based on ferritin; OR = 2.4; CI 95%: 1.02 - 5.5; $p < 0.05$ based on serum iron), birth asphyxia or neonatal distress (OR = 15.1; CI 95%: 1.9 - 123.6; $p < 0.002$; OR = 7.4; CI 95%: 1.5 - 36.3; $p < 0.008$ based on ferritin; OR = 4.6; CI 95%: 1.8 - 11.7; $p < 0.004$ based on serum iron) and neonatal hypoglycemia (OR = 3; CI 95%: 1.1 - 9.6; $p < 0.05$; OR = 3.5; CI 95%: 1.1 - 11.1; $p < 0.03$ based on ferritin; OR = 2.5; CI 95%: 1.2 - 5.4; $p < 0.04$ based on serum iron).

When the diagnosis of anemia was considered at 28 - 32 weeks of gestation, significant associations were found with Gestational diabetes (OR = 3.8; CI 95%: 1.1 - 14.7; $p < 0.05$), PROM (OR = 7.5; CI 95%: 1.9 - 62.4; $p < 0.04$), cesarean section (OR = 4.8; CI 95%: 1.7 - 13.4; $p < 0.003$), prematurity (OR = 5.3; CI 95%: 1.1 - 25.5; $p < 0.03$), birth asphyxia (OR = 10.9; CI 95%: 1.3 - 88.9; $p < 0.008$; OR = 3.7; CI 95%: 1.03 - 13.5; $p < 0.04$ based on ferritin; OR = 2.8; CI 95%: 1.1 - 7.5; $p < 0.05$ based on serum iron) and neonatal hypoglycemia (OR = 4.7; CI 95%: 1.2 - 17.9; $p < 0.02$).

At term, the diagnosis of anemia was significantly associated with GDM (OR = 9.2; CI 95%: 1.9 - 44.4; $p < 0.01$), PE (OR = 3.4; CI 95%: 1.1 - 11.9; $p < 0.05$), PROM (OR = 2.8; CI 95%: 1.1 - 9.8; $p < 0.05$ based on ferritin), cesarean section (OR = 6.03; CI 95%: 2.2 - 16.8; $p < 0.01$; OR = 2.1; CI 95%: 1.4 - 3.2; $p < 0.03$ based on serum iron), birth asphyxia (OR = 2.9; CI 95%: 1.03 - 8.03; $p < 0.05$ based on serum iron) and neonatal hypoglycemia (OR = 3; CI 95%: 1.01 - 9.6; $p < 0.05$).

As of oxidative stress diagnosed at recruitment, significant associations were found with PROM (OR = 9; CI 95%: 1.1 - 75.2; $p < 0.02$ based on oxidized LDL), cesarean section (OR = 3.7; CI 95%: 1.1 - 14.5; $p < 0.05$ based on SOD), prematurity (OR = 6.4; CI 95%: 1.3 - 31.2; $p < 0.02$ based on oxidized LDL), birth asphyxia (OR = 13.2; CI 95%: 1.6 - 108.2; $p < 0.004$ based on oxidized LDL) and neonatal hypoglycemia (OR = 2.6; CI 95%: 1.01 - 8.3; $p < 0.05$ based on oxidized LDL).

The diagnosis of oxidative stress at 28 - 32 weeks of gestation (based on oxidized LDL) was found significantly associated with acute fetal distress (OR = 4.2; CI 95%: 1.2 - 14.3; $p < 0.02$), cesarean section (OR = 2.9; CI 95%: 1.1 - 8.5; $p < 0.05$ based on SOD), LBW (OR = 9.9; CI 95%: 2.1 - 47.7; $p < 0.002$), birth asphyxia (OR = 3.9; CI 95%: 1.1 - 15.7; $p < 0.05$) and neonatal hypoglycemia (OR = 3.2; CI 95%: 1.01 - 10.3; $p < 0.04$).

For oxidative stress diagnosed at term, significant associations concerned GDM (OR = 11.4; CI 95%: 1.4 - 91.9; $p < 0.006$ as of SOD), PE (OR = 4.3; CI 95%: 1.1 - 16.8; $p < 0.03$ as of oxidized LDL), acute fetal distress (OR = 8.3; CI 95%: 1.7 - 39.8; $p < 0.003$ as of oxidized LDL), cesarean section (OR = 4.3; CI 95%: 1.5 - 12.6; $p < 0.007$ as of SOD), prematurity (OR = 6; CI 95%: 1.2 - 29.1; $p < 0.02$ as of oxidized LDL), LBW (OR = 4.3; CI 95%: 1.1 - 16.8; $p < 0.03$ as of oxidized LDL), birth asphyxia (OR = 12.4; CI 95%: 1.5 - 101.4; $p < 0.005$ as of oxidized LDL) and neonatal hypoglycemia (OR = 3.5; CI 95%: 1.03 - 11.9; $p < 0.04$ as of oxidized LDL).

Since various pre-pregnancy and pregnancy risk factors and factors related to iron absorption are likely to influence the occurrence of these outcomes, we registered them. Those significantly associated with adverse outcomes served to base adjustment analyses (adjusted OR) of associations.

GDM was significantly associated with intestinal parasitosis (OR = 3.8; CI 95%: 1.1 - 14.7; $p < 0.05$), geophagia (OR = 4.04; CI 95%: 1.3 - 12.8; $p < 0.02$) and with hypertension in the family (OR = 2.7; CI 95%: 1.1 - 7.6; $p < 0.05$). PE was significantly associated with intestinal parasitosis (OR = 3.8; CI 95%: 1.1 - 14.7; $p < 0.05$). Acute fetal distress was significantly associated with antecedent of diabetes in the family (OR = 5.5; CI 95%: 1.1 - 38.9; $p < 0.03$). Cesarean section was significantly associated with intestinal parasitosis (OR = 4.8; CI 95%: 1.7 - 13.4; $p < 0.003$), geophagia (OR = 4.6; CI 95%: 1.6 - 13.2; $p < 0.005$) and consumption of tannins and fibers (OR = 5.6; CI 95%: 1.9 - 15.8; $p < 0.002$). Prematurity, was significantly associated with geophagia (OR = 4; CI 95%: 1.2 - 13.4; $p < 0.03$) and consumption of tannins and fibers (OR = 4.2; CI 95%: 1.2 - 14.3; $p < 0.03$). Birth asphyxia (neonatal distress) was significantly associated with antecedent of precocious abortion (OR = 4.4; CI 95%: 1.2 - 15.8; $p < 0.03$), antecedent of macrosomia (OR = 8.9; CI 95%: 1.3 - 59.8; $p < 0.04$) and consumption of tannins and fibers (OR = 3.5; CI 95%: 1.02 - 12.2; $p < 0.05$).

Subsequently, adjusted OR showed significant links between GDM and SOD at the term (OR = 5.6; CI 95%: 1.01 - 52.6; $p < 0.05$), PE and Oxidized LDL at the

term (OR = 3.9; CI 95%: 1.1 - 15.8; $p < 0.05$), cesarean section and serum iron (OR = 0.03; CI 95%: 0.002 - 0.6; $p < 0.03$), LBW and Oxidized LDL at 28 - 32 weeks (OR = 8.2; CI 95%: 1.3 - 52.7; $p < 0.03$) and acute fetal distress and Oxidized LDL at term (OR = 10.9; CI 95%: 1.01 - 133.2; $p < 0.05$).

4. Discussion

Our study aimed to assess adverse pregnancy outcomes on all women having been routinely iron supplemented during pregnancy. So, the pending question might be: in what proportion can iron supplementation prevent as well as induce maternal and perinatal complications of oxidative stress?

Even though abundant literature has been claiming anemia strongly associated with adverse outcomes [17] [22] [23] [24], very few studies deal with complications other than prematurity, LBW, PE and GDM. So, our study is among the first to depict such a wide range including GDM, PE, PROM, cesarean section, prematurity, LBW, acute fetal distress, birth asphyxia and neonatal hypoglycemia.

Complications significantly associated with anemia at the beginning of pregnancy were prematurity, LBW, neonatal hypoglycemia and birth asphyxia. When the diagnosis of anemia was considered at 28 - 32 weeks of gestation, meaning absence of correction by iron supplementation, there were quite similar complications: prematurity, GDM, PROM, cesarean section and birth asphyxia. Persistence of anemia till the term worsens the neonatal status, which widens the field of complications with neonatal hypoglycemia. Our findings are in accordance with the fact that maternal anemia actually acts in conjunction with various risk factors in raising the odds of maternal and perinatal morbidity/mortality [5] [25] [26]. This could explain the associations of some outcomes with factors related to intestinal iron absorption, such as prematurity with geophagia and consumption of tannins and fibers, acute fetal distress with antecedent of diabetes in the family. However, other associations are more difficult to explain, such as cesarean section with intestinal parasitosis, geophagia and consumption of tannins and fibers, birth asphyxia (neonatal distress) with previous precocious abortion and consumption of tannins and fibers.

Trials have shown that adverse pregnancy outcomes are in accordance with the severity of maternal iron deficiency anemia [27]. In their systematic review and meta-analysis on hemoglobin concentration and pregnancy outcomes, Sukrat *et al.* [28] concluded that hemoglobin below 11 g/dl increases the risk of preterm birth, low birth weight, and small gestational age in the first trimester and the risk of low birth weight in the third trimester. Lieberman *et al.* [29] reported an increased odds ratio for preterm birth at Hb < 7 g/dl and hematocrit (Hct) from 41% to 44% had lowest risk of premature birth and double at Hct < 37%.

However, Rehema *et al.* [30] as well as Falahi *et al.* [31] noted no conclusive evidence that improvement of the iron status during the first and second trimes-

ter would improve the outcome of pregnancy. In our mind, this might suggest that only the pre-pregnancy status counts, at least dealing with prematurity and LBW. According to the Haider *et al.*'s review and meta-analysis of 48 randomized trials (17,793 women) and 44 cohort studies (1,851,682 women) [4], randomized trials tend to show a significant association of iron supplements with lower risk of LBW but not on prematurity, while the association involves both in cohort studies. The most concerned periods are the first or second trimesters.

Our study found significant association of GDM with anemia diagnosed at 28 - 32 weeks of gestation, suggesting a potential beneficial effect of iron supplementation if initiated at the beginning of pregnancy. Relationships of iron supplementation and GDM are still controversial. Nutritional iron intake has been found associated with risk of GDM [32]. Some studies found that dietary heme iron intake, but not non-heme iron intake, and supplemental iron intake increased the risk of GDM [33] [34]. Randomized controlled trials in Hong Kong [35] and in Finland [36] found no relationship. Authors who found that the risk was increased observed that it was most increased by high serum iron for some authors [37] [38] [39] [40] or by high ferritin for some others [23] [41] [42] [43]. The debate is still ongoing.

So, even though anemia was found significantly associated with most of complications known to be linked with it, in our series the effect of iron supplementation on pregnancy outcomes is far to be obvious. This could be owed to the fact that improvement of 9.01 - 9.6 g/dl observed among anemic women [5] might be too small to induce notable changes in outcomes. Furthermore, Viteri and Berger [44] suggest that maternal hemoglobin between 9.5 and 10.5 g/dl in the third trimester correlates with the best clinical outcome.

As we observed it in this study, outcomes found significantly associated with oxidative stress (mostly based on oxidized LDL) seem to overlap those linked to anemic condition. In the present series similarity between complications of anemia and that of oxidative stress is more observed at 28 - 32 weeks of gestation. This strongly suggests that major correction in both anemic and oxidative status should be initiated long before this landmark.

Whether these outcomes are solely related to anemia or oxidative-mediated is difficult to demonstrate. Indeed, irrespective of hemoglobin and iron status, maternal psychosocial or oxidative stress is known to enhance the risk of strictly maternal organic and non organic pathologies (infections, gastritis, hypertensive disorders, insomnia and depression) along with Infant's morbidity (LBW) [45] [46] [47].

5. Conclusion

Outcomes found significantly associated with oxidative stress seem to overlap those linked to anemic condition. Similarity between complications of anemia and that of oxidative stress is more observed at 28 - 32 weeks of gestation. This strongly suggests that major correction in both anemic and oxidative status should be initiated long before this landmark.

Limitation and Strength of the Study

The main limitation of our study relates to failure of our findings to demonstrate the precise part owed to either anemia or oxidative stress in generation of adverse outcomes observed. The strength of the study comes first from the wide range of outcomes studied in relation to maternal anemia and oxidative stress. Our study also allows to consider 28 - 32 weeks of gestation as an actual landmark for preventive measures against adverse outcomes associated with anemia and oxidative stress.

Author's Contributions

MMA is the principal investigator, participated in designing the study and was actively involved in data collection and statistical calculations. TUB generated and designed the study. He drafted the first manuscript. MMR participated in designing the study and analyzing the results. All authors contributed in preparing the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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