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Original Research Article

Folate Status of Pregnant Women in Katsina, North-Western, Nigeria

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Abstract: Maternal folate deficiency has been implicated in adverse outcomes for both mother and foetus and understanding of the levels of folate during pregnancy is necessary for rational intervention to prevent these adverse outcomes. Cross-sectional comparative study was conducted among 300 women (pregnant and non-pregnant) at Federal Medical Center, Katsina, Nigeria to determine folate status of pregnant women. Serum and red cell folate were determined with ELISA and immunoassay respectively. Data was analysed using SPSS version 20.0 and level of significance set at $p \leq 0.05$. Pregnant women had a mean serum and red cell folate of 28.11 ± 4.56ng/mL and 269.28 ± 77.79ng/mL whereas the corresponding values of non-pregnant women were 28.07 ± 5.01ng/mL ($p = 0.95$) and 270.82 ± 89.04ng/mL ($p = 0.86$) respectively. There was no significant difference in the prevalence of folate deficiency between pregnant and non-pregnant women using both serum ($\chi2 = 1.59$, $df = 8$, $p = 0.26$) and red cell ($\chi2 = 3.32$, $df = 8$, $p = 0.19$) folate, whereas anaemia is more common in pregnant women compared to non-pregnant women 67.5% versus 18% ($\chi2 = 18.2$, $df = 4$, $p = 0.03$). Among pregnant women, there is no significant difference in folate levels on basis of parity ($p = 0.08$) or gestational age ($p = 0.53$). Folate deficiency is not common among pregnant women in this environment. Therefore, the high prevalence of anaemia observed among pregnant women this study, further buttressed the need for identifying specific aetiology in all cases of anaemia in pregnancy.

Keywords: Pregnancy, Folate, Status, Anaemia, Nigeria, Katsina.

INTRODUCTION

Folic acid (folate) is essential for the regulation of cell division and growth especially during DNA synthesis and therefore very vital in haemopoiesis, infancy and pregnancy (Shaw GM *et al.*, 1995; Hoffbrand AV *et al.*, 2005; Scholl TO *et al.*, 2000). Pregnancy is a physiological state associated with increased demand for folate and as such its deficiency is common in pregnancy (Hoffbrand AV *et al.*, 2005; Fairbanks VF *et al.*, 2000). Folate deficiency causes anaemia in pregnancy and increases the risk of fetal malformation such as cardiac, limb, palate and neural tube defects (Fleming AF *et al.*, 1969; Hoffbrand AV *et al.*, 2001; Edward R 2006; Harrison KA *et al.*, 2001). Adequate folate intake during the pre-conception period and early in pregnancy protects against these complications (Hoffbrand AV *et al.*, 2001; Wilcox AJ *et al.*, 2007).

An understanding of the interplay between pregnancy and folate is important in planning rational therapeutic intervention for pregnant women. This is of particular importance in our environment where a combined effect of ignorance, poverty, malabsorption, multiple pregnancies, malaria and other infections as well as genetic conditions like haemoglobinopathies increases the risk of folate deficiency in pregnancy (Hoffbrand AV *et al.*, 2001; Edward R 2006). There has been no previous study on the levels and role of folate as a cause of anaemia in pregnancy in our centre. Thus, this study was conducted to determine the folate status of pregnant women attending Antenatal Clinic (ANC) at the Federal Medical Centre (FMC), Katsina, Katsina State, Nigeria.

MATERIALS AND METHODS

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This was a comparative cross sectional study involving 200 consecutively consenting pregnant women at various trimesters who access antenatal care at Federal Medical Centre, Katsina and 100 of their age and sex matched non- pregnant counterpart attending family planning clinic for the first time in the same hospital. The study was conducted from 1st April to 31st December, 2017. Breastfeeding women and those with sickle cell disease, hypertension, diabetes, human immunodeficiency virus, viral hepatitis and liver or renal diseases were excluded from the study. Non pregnant women on hormonal contraception and those with infertility, gynaecological bleeding disorder and any form of malignancy were also excluded.

Clinical data of participants (evidence of pregnancy, sickle cell disease, hypertension, diabetes, liver and renal disease and use of any medication including routine antenatal care drugs) were extracted from their hospital file.

Following standard venepuncture procedure, 6ml of venous blood was collected from each participant and 3ml each dispensed into Ethylene Diamine Tetra Acetic acid (EDTA) bottle for complete blood count (CBC), reticulocyte count and red cell folate and plain bottle for serum folate.

Samples for CBC and reticulocyte count were processed within 2 hours of collection with Sysmex XT 2000i haematology analyser. One hundred (100) µL of the well mixed EDTA sample was added to 3ml of prepared haemolysing reagent, mixed, allowed to stand for 90 minutes at room temperature and then stored at -20^0C for the determination of red cell folate using Cobas e411 immunoassay analyser. Sample in the plain bottle was allowed to stand for 2 hours, spurn, serum harvested and stored at -20^0C for determination of serum folate using ELISA kit (Wkea Med Supplies Corp. Changchun, Jilin, China) according manufacturer's instruction. Serologic tests for HIV, Hepatitis B and C were conducted on the serum of participants with Determine™ HIV-1/2 Ag/Ab Combo, Ascon and Healgen respectively while pregnancy test was done on early morning urine specimen of non-pregnant women using SURESIGN Pregnancy Test strip.

Data obtained was analysed using Statistical Package for Social Sciences (SPSS) version 20 (IBM Corp. Armonk, NY) and results presented as percentages and mean (± standard deviation).Data set was tested for normality using Kolmogorov-Smirnov, independent *t*-test and ANOVA were employed for comparison of mean values as appropriate while parametric (Pearson correlation) and non- parametric (Spearman and point biserial correlations) tests were used to test for association and the level of significant statistical relationship was set at $p < 0.05$.

Informed written consent was obtained from each participant and the study was approved by Hospital Committee on Research Ethics and Patients Protection.

Definition of Terms

Anaemia is defined as haemoglobin concentration less than 11g/dL. (WHO/UNICEF, 2004).

Criteria for folate deficiency are presence of serum and/or red cell folate of less than 5ng/ml and/or 140ng/ml respectively. (Fischbach F *et al.*, 2008).

RESULTS

The mean age of the pregnant women was 26.71±5.83 years with a range of 17 to 50 while that of non-pregnant women was 27.10 ± 5.54 years with a range of 18 to 50 ($p = 0.26$). Among pregnant women, 43 (21.10%), 83 (40.70%) and 78 (38.20%) were in their first, second and third trimesters respectively. Also 47 (23.04%), 80 (39.22%) and 77 (37.75%) of the pregnant women were primigravidae, multiparous and grand-multiparous respectively.

The mean serum and red cell folate of pregnant women were 28.11 ± 4.56ng/mL and 269.28 ± 77.79ng/mL while non-pregnant women had a mean serum and red cell folate of 28.07 ± 5.01ng/mL ($p = 0.95$) and 270.82 ± 89.04ng/mL ($p = 0.86$) respectively (Table 1). Pregnant women had a mean Haemoglobin concentration and reticulocyte count of 10.2±1.9g/dL and 3.9±2.4% while the corresponding mean values of non- pregnant women were 12.2±1.2g/dL ($p = 0.01$) and 1.9±0.8% ($p = 0.03$) respectively. Folate levels, haematocrit, reticulocyte count and red cell indices of participants are shown in the Table 1.

The prevalence of folate deficiency among pregnant women using both serum and red cell folate was 0.9% and that of non-pregnant women were 2% for serum ($\chi^2 = 1.59$, $df = 8$, $p = 0.26$) and 3% for red cell folate (($\chi^2 = 3.32$, $df = 8$, $p = 0.19$) respectively (Table 2) while the prevalence of anaemia among pregnant women was 67.5% against 18.0% among non-pregnant women ($\chi^2 = 18.2$, $df = 4$, $p = 0.03$) as presented in Table 2. Comparison between folate levels of pregnant women and their gestational age as well as parity are depicted in Table 3 and revealed that, although the red cell folate decreases with increasing parity, this change was not statistically significant ($p = 0.08$) and no significant difference in red cell folate across the three trimesters ($p = 0.53$). Both age ($r = 0.18$, $p = 0.03$) and folic acid supplementation during index pregnancy ($r_{pb} = 0.15$, n = 200, $p = 0.04$) had a week positive correlation with red cell folate (Table 4).

Table 1: Folate levels, haemoglobin, reticulocyte count and red cell indexes of the participants

parameter	Pregnant women N = 200 Mean ± SD	Non pregnant women N = 100 Mean ± SD	*P* - value
Serum folate (ng/mL)	28.11 ± 4.56	28.07 ± 5.01	0.95
RBC folate (ng/mL)	269.28 ± 77.79	270.82 ± 89.04	0.86
Haemoglobin (g/dL)	10.2 ± 1.9	12.2 ± 1.2	0.01
Retic (%)	3.9 ± 2.4	1.9 ± 0.8	0.03
MCV (fL)	80.2 ± 5.9	81.2 ± 6.7	0.19
MCH (pg)	28.2 ± 4.1	28.6 ± 2.4	0.39
MCHC (g/dL)	35.3 ± 4.3	35.2 ± 2.0	0.80
RDW (%)	18.9 ± 5.0	19.3 ± 6.7	0.76

RBC = Red Blood Cell, Retic = Reticulocyte count, MCV = Mean Cell Volume, MCH = Mean Cell Haemoglobin, MCHC = Mean Cell Haemoglobin Concentration, RDW = Red cell Distribution Width

Table 2: prevalence of folate deficiency and anaemia among participants

Parameter	Pregnant women Frequency (%)	Non pregnant women Frequency (%)	$\chi 2$	*df*	*P* - value
Serum folate					
Low	2 (0.9)	2 (2.0)			
Normal	167 (81.9)	85 (85.0)			
High	35 (17.2)	13 (13.0)			
Total	200 (100.0)	100 (100.0)	1.59	8	0.26
Red cell folate					
Low	2 (0.9)	3 (3.0)			
Normal	198 (97.0)	96 (96.0)			
High	4 (1.9)	1 (1.0)			
Total	200 (100.0)	100 (100.0)	3.32	8	0.19
Haemoglobin					
Low	135 (67.5)	18 (18.0)			
Normal	66 (32.5)	82 (82.0)			
Total	204 (100.0)	100 (100.0)	18.21	4	0.03

Reference Range for serum folate = 5-21ng/mL. (Fischbach F *et al.*, 2008). Reference Range for red cell folate = 140-628ng/mL. (Fischbach F *et al.*, 2008). Reference Range for haemoglobin = 11-12.5g/dL (WHO/UNICEF, 2004).

Table 3: Comparison between folate levels and gestational age and parity of the pregnant women

Parameter	Serum folate (ng/mL)	Red cell folate (ng/mL)
Gestational age		
First trimester (N = 43) Mean ± SD	28.39 ± 3.60	280.34 ± 84.85
Second trimester (N = 83) Mean ± SD	27.66 ± 5.35	264.50 ± 73.56
Third trimester (N = 78) Mean ± SD	28.40 ± 4.21	263.49 ± 77.94
P - value	0.54	0.53
Parity		
Primigravidae (N = 47) Mean ± SD	29.04 ± 3.13	266.58 ± 63.39
Multipara (N = 80) Mean ± SD	27.59 ± 5.06	272. 67 ± 76.70
Grand multipara (N = 77) Mean ± SD	28.15 ± 4.66	267.16 ± 86.47
P - value	0.24	0.08

Table 4: Association between folate levels and socio-demographic and clinical characteristics of the pregnant women

Parameters	Serum folate		Red cell folate	
	Correlation co-efficient	***P* - value**	**Correlation co-efficient**	***P* - value**
Age (*r*)	-0.08	0.91	0.18	0.04
Tribe (rho)	0.07	0.30	0.08	0.27
Religion (r_{pb})	0.08	0.26	0.05	0.52
Education status (rho)	-0.11	0.12	0.03	0.65
Occupation (rho)	-0.09	0.16	0.09	0.21
Husband occupation (rho)	-0.01	0.99	0.05	0.51
Parity (rho)	0.03	0.66	-0.05	0.47
Gestational age (*r*)	-0.03	0.63	0.059	0.40
Last child birth (rho)	-0.02	0.81	-0.05	0.50
History multiple gestation (r_{pb})	-0.01	0.99	0.04	0.57
Neural tube defect (r_{pb})	-0.08	0.28	-0.09	0.90
History of abortion (r_{pb})	0.04	0.58	0.10	0.15
Folic acid supplement (r_{pb})	0.02	0.74	0.15	0.04
Iron supplement (r_{pb})	0.05	0.48	0.13	0.06

r = Pearson correlation, rho = Spearman correlation, r_{pb} = Point biserial correlation

DISCUSSION

Folate requirement increases by about three to six fold in pregnancy and lactation with attendant risk of its deficiency especially in women not taking adequate supplementation (Hoffbrand AV *et al.*, 2005; Wilcox AJ *et al.*, 2007).

The majority of the participants in this study had normal folate levels and only 6.8% (both pregnant and non-pregnant) of them were folate deficient using either serum or red cell. This finding is in contrast with studies from Gombe North-East, Nigeria and Sri Lanka that reported prevalence of folate deficiency among women of 15% and 43% respectively (Dorothy JV *et al.*, 2007; Thoradeniya T *et al.*, 2006). Also, the mean folate levels of our participants were higher than that reported from North Eastern, Nigeria and Ahmadbad, India (Dorothy JVet al.,2007; Arpita PP et al., 2012).All these differences could be explained by the fact that this study was carried out at a tertiary hospital in an urban area as against others that involved both urban and rural women leading to a disparity in the socio-economic status of the participants and alternatively the time elapsed since their studies might have witnessed the widespread compliance with public health measures such as food fortification targeted at eliminating the folate deficiency in the general population.

This study did not find any significant difference in folate levels between pregnant and non-pregnant women unlike a study from Bangladesh, which showed serum folate of pregnant women was higher than that of non-pregnant women. (Karim KM *et al.*, 2009). Although the red cell folate level decreased with increasing parity, this change was not statistically significant, but may suggests depletion of folate stores due to both maternal and foetal demand that increase as the pregnancy increases in gestational age. The serum folate level in the first and third trimesters was higher than that of second trimester and this is also contrary to the study by Karim et.al, in Bangladesh, which showed that serum folate increases as the pregnancy advances in gestational age. (Karim KM *et al.*, 2009). The weak but statistically significant positive correlation between folic acid supplementation during index pregnancy and RBC folate level among participants in our study was previously reported by other studies and this implies that taking folic acid supplement may increase the levels of RBC folate (Ukiba SN *et al.*, 2013; Idowu OA *et al.*, 2005; Nwizu EN *et al.*, 2011; Akinyinku OO *et al.*, 2004).

Our findings of lower mean haemoglobin concentration and higher prevalence of anaemia among pregnant women compared to controls are in keeping with findings of several independent studies across the country and can be further buttressed by the WHO report which showed that anaemia affects two-third of all pregnant women in Sub-Saharan Africa (WHO/UNICEF 2004; Dorothy JV *et al.*, 2007; Isah HS *et al.*, 1985). Anaemia in pregnancy especially in developing countries arises from multiple causes including iron and folate deficiency, malaria and hookworm infestation, infections such as HIV and haemoglobinopathies while in developed countries physiological haemodilution is the main cause (WHO/UNICEF 2004; Pathak P *et al.*, 2004).

Although the prevalence of anaemia is higher among pregnant women compared to their non pregnant counterparts in this study, majority of the pregnant women had normal folate levels. This high prevalence of anaemia in the setting of normal folate level could arise from other causes of anaemia like physiologic haemodilution, iron and other micronutrient deficiencies arising from poor appetite, vomiting and

low socio-economic status as well as malaria, hookworm infestation and many other infections. As all these mentioned causes of anaemia are common in our environment, so their role in the in the causation of anaemia in pregnancy should not be over looked.

LIMITATIONS

The setting of the study as a hospital based and its inability to determine the levels of other nutrients like iron and vitamin B12 to established the actual cause of anaemia in pregnancy.

CONCLUSION:

Anaemia in pregnancy is common among pregnant women accessing ANC in FMC Katsina even though majority of the pregnant women had normal folate levels. Thus the cause of anaemia in these subjects is due to causes other than folate deficiency. We therefore, recommend detailed evaluation of all pregnant women presenting with anaemia to identify the specific cause.

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