

Folic acid Deficiency and risk of Prematurity

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الخلاصة

لتحديد أو اثبات وجود علاقة بين نقص الفولك اسد وخطر الولادة المسبقة. تم إجراء الدراسة في مستشفى الزهراء للولادة والأطفال في النجف للفترة ما بين كانون الثاني ٢٠٠٧ ولغاية تشرين الأول ٢٠٠٧. تم اختيار ستون مريضة بطريقة عشوائية وتم تقسيمهم إلى مجموعتين تضم المجموعة الأولى ٣٠ مريضة في حالة ولادة مسبقة أي أقل من ٣٧ أسبوع للحمل بينما تضم المجموعة الثانية ٣٠ مريضة ولكن بفترة حمل كاملة بين ٣٧-٤٢ أسبوع للحمل. تم تعريف حالات فقر الدم بحسب تعريف منظمة الصحة العالمية بأن تكون نسبة الهيموغلوبين في الدم أقل من ١١ غم/دل وأيضا تعتبر المريضة مصابة بفقر دم نقص الفولك اسد عندما تكون نسبته في الدم أقل من ١١ نانومول/ل.

أظهرت النتائج ان من بين النساء اللواتي لديهن حالة ولادة مسبقة فان ٥٦.٦ % لديهن نسبة هيموغلوبين في الدم تتراوح بين ٨-١٠.٩ بينما المريضات في حالة الحمل التام فان ٤٠ % منهن فقط لديهن نسبة الهيموغلوبين تتراوح بين ٨-١٠.٩. كما أظهرت الدراسة ان اغلب حالات الحمل الكامل ٥٣.٣ % لديهن نسبة الهيموغلوبين في الدم مساوية أو أكثر من ١١ غم/دل. كما أظهرت الدراسة وجود فرق كبير في نسبة الفولك اسد في الدم بين المجموعتين. بينت الدراسة أيضا ان معدل الفولك اسد في الدم في المجموعة الأولى هو ١٦.٦ + ١.٢ بينما في المجموعة الثانية فان معدل الفولك اسد هو ٢٢.١ + ٤.٠ نانومول/ل. نستنتج من هذه الدراسة بان هناك زيادة في حدوث الولادة المسبقة عند النساء الحوامل اللواتي يعانون من نقص الفولك اسد في الدم لذلك ينصح بتناول هذه المادة خلال فترة الحمل.

Summary:

The objective of this study was to determine the association between folic acid deficiency and prematurity and its magnitude in women in their third trimester of pregnancy the study was done at Gynecology & Obstetric department, Al_Zahra'a teaching hospital, Al_Najaf, Iraq. sixty women were randomly selected and sub

grouped in to 1st group preterm delivery(<37week of gestation at delivery) were defined as study group (n=30), while 2nd group defined as term pregnancy (between 37 _42/52) weeks of gestation as a control group, (n=30).

The study shows that women in preterm labor (56.6%) have Hb concentration between 10.9_8 gm/dl while 40% in term pregnancy have the same Hb & most women in term pregnancy (53.3%) have Hb concentration >or=11gm/dl. Also the study showed significant differences between s. folate in two the groups (p<0.01) & mean s. folate in preterm group 16.6± 1.2 nmol/l while in control group mean s.folate 22.1±1.4nmol. According with these results, there is a risk of prematurity in pregnant women with folic acid deficiency, therefore, the consumption of this micronutrient during the pregnancy is important to reduce complication of prematurity.

Introduction:

PTL is defined as labor which occurs from the viability of fetus (currently defined in the UK as 24 completed weeks of gestational age from the first day of last menstrual period assuming 28 days menstrual cycle or 22 completed weeks from the date of conception if it is accurately known) until the completion of the 37th weeks of gestation (1). PTL with intact membrane at presentation makes up at least half of the cases of preterm labor (2). Preterm birth and low birth weight (LBW, <1500grms) continue as the commonest cause of excess perinatal morbidity, mortality and excess birth related costs and medical

malpractice liabilities worldwide.(3) "The aetiology of preterm labour remains unknown, prediction lacks specificity, prophylaxis is unhelpful, diagnosis is difficult and the benefits and risks of tocolytic therapy are still being debated"(4), It has been estimated that the incidence of preterm delivery varies from 5% to 10% of all births in developed countries, and that spontaneous preterm labour in otherwise uncomplicated singleton pregnancies accounts for between one third and one half of all preterm deliveries.^{5 6} In 1997, in England and Wales, 50.3% of all neonatal deaths were due to immaturity.⁷ The costs of neonatal intensive care in the short term and the resources needed to support children with long term morbidity as a result of preterm birth are considerable.

Preterm labour is more common in smokers, teenagers, drug abusers, women with bacterial vaginosis, multiple pregnancy, and women who have previously delivered preterm.(8)

Folic acid, or pteroylglutamic acid, is a well-known water soluble vitamin of the B-complex group. It is necessary for DNA synthesis and normal erythropoiesis. Apart from increased demand, folate deficiency can occur in malnutrition, malabsorption, chronic hemolytic anemias, chronic alcoholism, repeated hemodialysis, and unusual dietary situations like total parenteral nutrition. The use of certain antiepileptic, antimalarial, antimicrobial and anticancer drugs may interfere with the absorption, conversion or utilization of folate leading to megaloblastic anemia.

The primary therapeutic indication is in the prophylaxis and treatment of deficiency states. Pharmacological supplementation is recommended in situations like pregnancy (for preventing macrocytic anemia, occurrence or recurrence of neural tube defects, counteracting teratogenic effect of anticonvulsants, *etc.*), malnutrition, malabsorption and chronic hemodialysis. It may be supplemented during lactation, in infants, the elderly, alcoholics, and in renal failure patients (9,10). Man cannot synthesize folic acid and hence must necessarily obtain it from food. The human body requires only small quantities of folate, but this is vital to various metabolic pathways, including DNA synthesis and normal erythropoiesis (11,12)..

The most common true anemias during pregnancy are iron deficiency anemia (approximately 75%) and folate deficiency macrocytic anemia, both of which are more common in women on inadequate diets and not receiving prenatal iron and folate supplements. A hemoglobin level less than 6 g/dL is generally associated with poor pregnancy outcome and may be complicated by prematurity, spontaneous abortions, low birth weight, and fetal deaths (13).

Low concentrations of dietary and circulating folate are associated with increased risks of neural tube defects, fetal growth retardation. preterm delivery and low birth weight infants. Further, high maternal homocysteine concentrations, a potential metabolic effect of folate deficiency, has been associated with habitual abortion, placental abruption and pre-eclampsia, which further increase the risk of poor pregnancy outcome and of low birth weight . Affected offspring may continue to have problems in later life (14).

Patients and method:

The study conducted at department of Gynecology and Obstetrics, Al-Zahra'a Teaching hospital, Najaf, Iraq from January 2007 till October 2007. We select 30 patients women with preterm labour, defined as regular uterine contraction at least one contraction in 10 minutes with documented changes in cervical dilatation 1-4

centimeters or effacement 25% or more with intact membranes before 36 completed weeks were enrolled in this study as a study group (group-1-). Thirty patients in labour at term defined as women with completed 37 weeks till 42 weeks of pregnancy included in the study as a control group (group-2-).

Patients with signs of placental abruption, chorioamnionitis, severe preeclampsia, rupture of fetal membranes, previous use of tocolytics therapy, serious maternal disease as cardiovascular disease or thyrotoxicosis, intrauterine growth restriction, fetal death or congenital anomalies of fetus were excluded from the study. Detailed history was obtained including obstetrical history as previous PTL any risk factor for cervical incompetence like previous operation to the cervix, elective termination, history of abdominal trauma, a physical fatigue smoking and no. of cigarette and history of documented uterine anomalies complete physical examination including uterine contraction and fetal heart monitoring was performed and repeated periodically. Information about food habit and any intake of folate supplement. At labour 10 ml of venous blood were obtained in a EDTA containing tube to perform a complete blood count CBC using an electronic counter Cobas Helios 3a (Roche Diagnostic Systems). Blood sample was analyzed at main hospital laboratory within a 2-hour period after aspiration. By using WHO criteria (1), maternal anemia was defined as Hb less than 11 g/dL in any stage of gestation. Serum folate was measured in this research. We used a Folate Radioassay Kit [125 I] (ICN Pharmaceuticals, Orangeburg, N.Y, USA). FD was defined when serum folate level was lower than 11 nmol/l, while normal s. folate level between 11_57 nmol/l.

Results:

During the period of this study, from January 2007-october 2007, 60 women were enrolled in this study aging between 15_40 year, these cases were subdivided in to: Group-1- women with preterm delivery and Group-2- women with full term delivery. The study shows that highest percentage of women with preterm labour (56.6%) have Hb concentration 10.9_8 gm/dl while in term pregnancy (40%) have the Hb concentration between 10.9_8 gm/dl. Regarding women who are not anemic (Hb \geq 11 gm/dl) 53.3% in term pregnancy and only 33.3% in group -1- have normal Hb concentration & P value was <0.01 which is statistically significant.

Table1: Difference in haemoglobine concentration (gm/dl) between the two groups

Hb%	Study group		Control group	
≥ 11 gm/dl	10	33.3%	16	53.3%
10.9_8	17	56.6%	12	40%
< 8 gm/dl	3	10%	2	6.65

P \leq 0.01

We can observe that percentage of women in group -1- with normal s. folate level (11_57 nmol/l) were 63.3% while in group -2- (control) 83.3% have normal s.folate. Percentage of women in preterm labor with s.folate < 11 nmol/l were 36.6% while in control group 16.6% have folate deficiency, which is statistically significant. (P <0.01).

Table 2:Comparison between serum folate in study and control groups

	Serum folate 11_57nmol/l		<11nmol/l	
Study group	19	63.3%	11	36.6%
Control group	25	83.3%	5	16.6%

p<=0.01

The mean s.folate in study group was 16.6+/- 1.2while in control group 22.1+/-1.4, which was statistically significant

Table 3:s.folate level between study and control group

	Mean s.folate -+s.d
Study group	16.6+/-1.2
Control group	22.1+/-1.4

P<0.01

Discussion

Anemia is the main hematological complication during pregnancy. According to the World Health Organization (WHO)(15), the diagnosis of anemia during pregnancy is established when the hemoglobin (Hb) level is below 11 g/dL, being this the borderline between "physiologic anemia during pregnancy" and true anemia during pregnancy. All over the world, anemia during pregnancy is a public health problem(16,17). The nutritional anemia is the most important cause of maternal anemia. Folate deficiency (FD) is considered as the second cause of nutritional anemia. Our study shows that (56.6%) of preterm patient have Hb concentration between 10.9_8 gm/dl,while (40%) in term patient have the same Hb concentration. The study showed that there is a significant differences between the two groups, P<0.01. This support that anemia may be a risk factor for prematurity. Our finding is in consistent with Klebanoff & Co-worker (1991) (18) and Kadyrov and CO-worker (1998) (19) have provided evidence that maternal anemia influences placental visualization by altering angiogenesis during early pregnancy. The findings of our study support hypothesis that folic acid deficiency (FD) during pregnancy, evaluated during third trimester, and at labor, is a risk factor for prematurity. Our results have concordance with what Sifakis and Pharmakides (13) stated about the fact that FD is more common in women who are not receiving prenatal folic acid supplements. The mechanisms which could explain the association between FD and prematurity that's Folic acid plays an important role in the

conversion of homocysteine in methionine (20). The relationship between serum folate and homocysteine may be useful for detecting borderline folic acid deficiency in pregnancy (21). A metabolic effect of folic acid deficiency is an elevation of blood homocysteine, so, total homocysteine (tHcy) measured in serum or plasma is a marker of folate status. Therefore, the biological plausibility could be explained using the possibility of occurrence of hyperhomocysteinemia. Epidemiological studies have shown that increased serum homocysteine concentrations well inversely correlated with folate concentrations (22). Increased circulating total homocysteine concentrations are associated with higher risk for premature vascular disease. Since, hyperhomocysteinemia disturbs the vascularization of the placenta and thereby reduces its function.(23,24).

Conclusion:

We conclude that folic acid deficiency may be associated with many complications during pregnancy and the consumption of this micronutrient during pregnancy is important to reduce complication including prematurity.

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