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Vitamin D Assessment In Iron Deficiency Anemic Pregnant Women and Their Newborns

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VITAMIN D is a prohormone nutrient, which is involved in skeletal and extra-skeletal functions. Iron is another essential nutrient that is necessary for the production of red blood cells and oxygen transport. This element plays important roles in enzymatic systems including those required for Vitamin D activation. Iron deficiency anemia (IDA) is one of the most common diseases among pregnant women worldwide. Vitamin D deficiency (VDD) during pregnancy might be associated with some adverse effects on fetal growth. Thisstudy was designed to assess the possible relationship between IDA in pregnant mothers, their corresponding newborns and vitamin D deficiency (VDD).

Research Design and Methods Maternal and fetal serum25-hydroxy vitamin D levels were evaluated using radioimmunoassay (RIA) technique, in 25 pregnancieswith IDA compared to 15 age-matched uncomplicated term gestations. Birth weight and clinical status of the neonateswere assessed.

Results The present study revealed that 25-hydroxy vitamin D level was statistically decrease in IDA pregnant group in comparison to the control group (p<0.001). Newborn birth weight of IDA group is significantly lower than the control group (0.05). The 25-hydroxy vitamin D is directly proportional to birth weight in the two groups (NHCG; p<0.0001; IDAG; p<0.001). The relationship of vitamin D levels between mothers and infants in both the IDA group and the control group was significant (p< 0.001).

Conclusion The present study reveals a high significant decrease of vitamin D level in women with IDA in comparison to the control. In addition, maternal vitamin D deficiency is associated with its deficiency in newborns; that might be reflected on .their lower birth weight

Introduction:

Pregnancy is a critical time in the lifecycle of a woman where she is responsible not only for her own well-being, but also that of her developing fetus, a process that continues during lactation. Until recently, the impact of vitamin D status during this period had not been fully appreciated. Data regarding the importance of vitamin D in health have emerged to challenge traditional dogma, and suggest that vitamin D – through its effect on immune function and surveillance – plays a role beyond calcium and bone metabolism on the health status of both the mother and her fetus(Wagner et al., 2012).

Iron deficiency anaemia (IDA) is also a common problem in pregnancy. Anemia is defined as hemoglobin of <11 g/dL in the first and third trimester and <10.5 g/dL in the second trimester (Milman, 2008).Anemia in pregnant women has been regarded as detrimental to the fetal growth and pregnancy outcome (Kumar *et al.,* 2013).

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Deficiencies in both Vitamin D and iron are recognized as two major public health concerns in the globe. Nearly, 30%–50% of all age groups are Vitamin D deficient worldwide (Ernst et al., 2015)

A significant association between vitamin D deficiency and anemia has been reported throughout the world (Sim et al., 2010). Several studies in various populations all over the world suggest a high degree of association between Iron deficiency anemia and vitamin D deficiency. Vitamin D receptor has already been reported in bone marrow and levels of 1, 25-dihydroxyvitamin D (1, 25-(OH) 2D) (active form of vitamin D) is several hundred folds higher in bone marrow compared to plasma (Kiss et al., 2011).

It imparts an important role in erythropoiesis the mechanism of Red Blood Cell (RBC) formation. Several mechanisms have been proposed to explain the association of vitamin D deficiency and anemia. Vitamin D influences Hemoglobin levels through a direct effect on erythropoiesis. Erythroid precursors are directly stimulated by vitamin D suggesting the latter's immense role in erythropoiesis. The storage and retention of Iron and reduction of pro-inflammatory cytokines is also aided by vitamin D (Bacchetta et al., 2014).

Thus vitamin D deficiency reduces the ability of RBCs to become active. Vitamin D possibly modulates the level of systemic cytokine production, thus reducing the inflammatory milieu leading to anemia of chronic diseases. Absorption of vitamin D may be impaired due to Iron deficiency in the same way it impairs fat and vitamin A intestinal absorption. It is still controversial which deficiency causes the other but this association should be addressed in view of better treatment proposal (Norman et al., 2006).

We aimedto detect a potential relationship between vitamin D deficiency and iron deficiency anemia in pregnant women and to compare the vitamin D maternal and their newborns levels with birth weight of the babies who were born to mothers with and without anemia.

Subjects and Methods:

Subjects:

The current study was carried out during the onset of labor on 25 pregnant women withIDA and 15 normal healthy pregnant women, all of whom get birth of singleton newborns. These women were recruited from the Obstetrics and GynecologyHospital, AinShamsUniversity. All the participating women gave informed consents preliminary to the study. Informed parental consent was obtained for all infants. The design of the study was approved by the Ethical Committee of our institute (Atomic Energy Authority).

The studied cases fulfilled the criteria of being 21 - 41 years old, para 1- 4, pregnant 37-40 weeks and were of the same socioeconomic status. The gestational age was assessed by the last menstrual period and confirmed by ultrasound done during the first trimester of pregnancy.

The studied cases had no past or present history of diabetes, hypertensioncerebro-vascular disease, or apparent endocrinopathy. Multiple pregnancies or pregnancies with fetal chromosomal abnormalities, congenital malformations were excluded from the study. Maternal smoking is known to be associated with various prenatal complications such as low birth weight, lower iron fetal stores, placental abnormalities such as decreased intervillous blood flow, altered uteroplacental flow (Monheitet al., 1984and Patevaet al. 2015), thus smoking women were also excluded. Also pregnant females with chronic infections or inflammations were excluded as chronic diseases affect the levels of ferritin (Matthew and Jason, 2013).

These cases were then categorized into 2 main groups:

Normal healthy control group (NHCG): comprised 15 women, their ages ranged between 21-38 years. They had normal uncomplicated term (37-39) singleton gestations. The controls were normotensive and free of risk factors.

The control newborn infants are categorized as (NHCN) where (n =15).

Pregnancies with IDA (IDAG): consisted of 25 pregnant women with IDA. They have iron deficiency anemia. The diagnosis of IDA is confirmed by the findings of low iron stores and a hemoglobin level less than 11g/dL (Matthewand Jason, 2013).

A serum ferritin level was obtained in patients with anemia and a mean corpuscular volume (MCV) less than 95 μm^3. Ferritin reflects iron stores and is the most accurate test to diagnose iron deficiency anemia. Although levels below15 ng/mL (33.70 pmol per L) are consistent with a

diagnosis of iron deficiency anemia, using a cutoff of 30 ng per mL (67.41 pmol per L) improves sensitivity from 25 to 92 percent, and specificity remains high at 98 percent. Alperet al., 2000 used a ferritin level of 12 mg per dL as the cutoff for iron deficiencyanemia.Ferritinvalues greater than or equal to100 ng/mL (224.70 pmol per L) generally excludes iron deficiency anemia (Matthew and Jason, 2013).

The studied groups were subjected to the following:

Full medical and obstetric history.

Thorough Clinical examination; with stress on maternal blood pressuremeasured with a standard mercury sphygmomanometer on the right arm after the subjects had been resting in thesupine position for at least 5 minutes. Since suboptimal vitamin D levels are linked with development of hypertension (Santoro*et al.,* 2015).

Apgar scores for each infant was assessed. Neonatal birth weightwasmeasuredusing *Secagmbh RCO kg Germany model 334/132108, max 10/20kg/d 5/10g.*

Blood sampling and assay:

Maternal blood (10 mL) was obtained in the non-fasted state at entrance to the hospital for delivery. A 10 mL cord blood sample was obtained at delivery from their corresponding mothers. Serum was separated and stored at −80° C until analysis.

Maternal and neonatalhemoglobin and hematocrit were analyzed. For MCV; draw a 3ml of the obtained blood into the tube containing anticoagulant and mixed well. Hemoglobin determinations were usually be performed by an automated cell counter from a tube of well-mixed EDTA-anticoagulated blood filled to a predetermined level (Billet, 1990).

Serum ferritin was measured with the use of ELISAs from Ramco Laboratories (Ramco Laboratories Inc.), and serum iron was measured with the use of graphite furnace atomic absorption spectrophotometry (Perkin Elmer Analyst 800;Perkin Elmer).

Vitamin D: 25(OH)D was measured using the Diasorin RIA (DiasorinInc, Stillwater, MN) by Quest Laboratories (that participate in the vitamin D External Quality Assessment Scheme (DEQAS)). In accordance with the recent Institute of Medicine DRI for vitamin D, vitamin D deficiency was defined as 25(OH)D < 12 ng/mL. The 2010 DRI committee reported that a 25(OH)D> 20 ng/mL was sufficient to meet the needs of 97.5% of healthy individuals (Institute of Medicine, 2011).

Statistical analysis: Data are expressed as mean ± standard deviation (SD) in the different groups. Means of different groups were compared using Student's *t* test. The differences between groups were evaluated using χ^2 tests for qualitative data.Relationships between hemoglobin, 25(OH) Dand dependent variables were assessed by simple linear regression analysis, and Pearson (r) correlation coefficients were presented. The results were considered significant whenever *p* values < 0.05 and highly significant when *p* values < 0.001 were observed. The statistical calculations were done usingStatgraphics plus (5) and the representations were done using Microsoft Excel (2010).

Results

The results of the current study were represented in Tables 1-4 and Fig. 1-2.

NHCG: Normal healthy control group. IDA: Iron deficiency anemia group.

NS: non-significant. *P*<0.05: is considered significant. *P*>0.05is considered non-significant

Itshows the maternal and neonatal data in different studied groups. As expected from matching criteria, the pregnant group with IDA did not differ from the control group as regards to maternal age, gestational age, gender, percentage of Cesarean section and Apgar score. Neonatal birth weight belongs to IDA pregnant women was significantly lower than the control group *(p<0.05)*.

It clarifies significant lower levels in IDAG compared to NHCG as regards HBG concentration, MCV and ferritin concentrations. Those results confirmed the diagnosis of IDA.

It demonstratessignificant lower levels of 25-OH (D) among maternal and neonatal IDA groups when compared to controls.

It demonstrates positive significant correlation between maternal 25-OH (D) and their corresponding neonatal birth weight.

TABLE 1. Maternal and neonatal data in the two studied groups

	NHCG Mean± SD n=15	**IDAG Mean± SD n= 25**	**Pvalue**
Maternal age (years)	26.87±4.1	26.72±3.9	NS
Gestational age (weeks)	38.4± 1.1	38.7± 1.2	NS
Parity	2.4 ± 1.12	2.44 ±1.08	NS
Gender (male) *n (%)*	26%	29%	NS
Cesarean section*(%)*	20%	23%	NS
Apgar score	8± 0.5	7±1	NS
Birth weight (gm)	3336.7±287.5	2584.0±123.1	< 0.05

NHCG: Normal healthy control group. IDA: Iron deficiency anemia group.
NS: non-significant. *P*<0.05: is considered significant. *P*>0.05is considered non-significant

TABLE 2. The mean values of maternal HBG, MCV and ferritin in NHCG and IDAG

	NHCG Mean± SD n=15	IDAG Mean± SD n= 25	*Pvalue*
Maternal HBG (g/dl)	12.33± 0.40	10.05± 0.29	<0.05
Maternal MCV(μm^3)	98± 0.73	73.4±1.47	<0.05
Maternal ferritin (ng/mL)	12.9± 0.45	10.36 ±0.78	<0.05

HBG: hemoglobin concentration. MCV: mean corpuscular volume.

TABLE 3. Mean values of 25-OH (D) in (NHCG) and (IDAG) and their newborns

	NHCG Mean± SD n=15	IDAG Mean± SD n= 25	*Pvalue*
Maternal 25-OH(D) (ng/ml)	30.75±1.12	19.8±2.9	<0.001
Neonatal 25-OH(D) (ng/ml)	17.5± 2.23	8.8± 1.89	<0.001

P<0.001is considered highly significant

TABLE 4. Correlation between maternal 25- OH and their corresponding neonatal birth weight

	Maternal 25-OH(D) (ng/ml) Mean± SD	Neonatal Birth Weight (gms)	r	*p value*
NHCG(n=15)	30.75±1.12	3336.7±287.5	0.5777	<0.0001
IDAG(n=25)	19.8±2.9	2584.0±123.1	0.6334	<0.001

P<0.0001is considered very highly significant

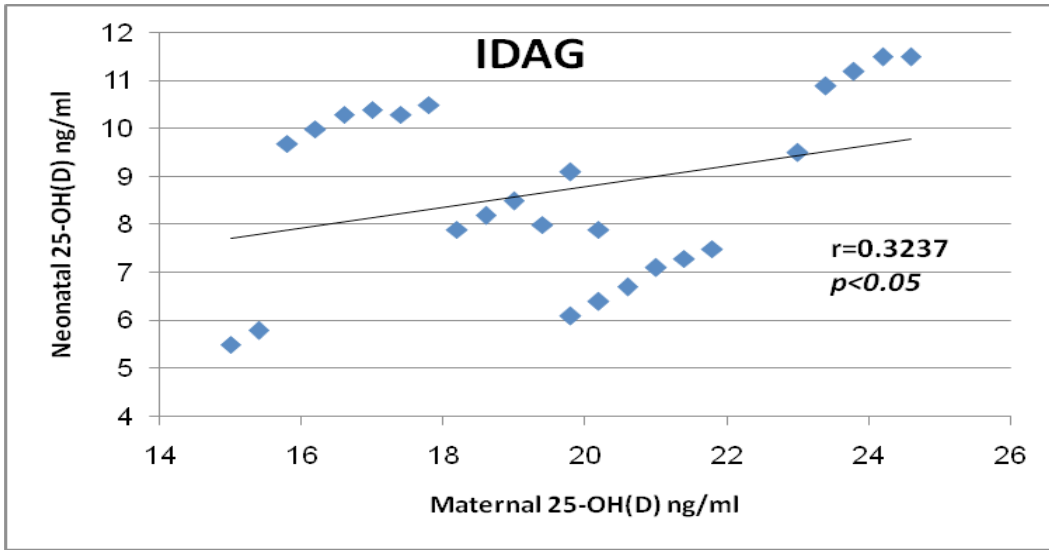

Fig. 1. correlation between maternal 25-OH (D) and corresponding neonatal 25-OH (D) in IDAG.

It reveals significant positive correlation between maternal 25-OH (D) and corresponding neonatal 25-OH (D) in IDAG

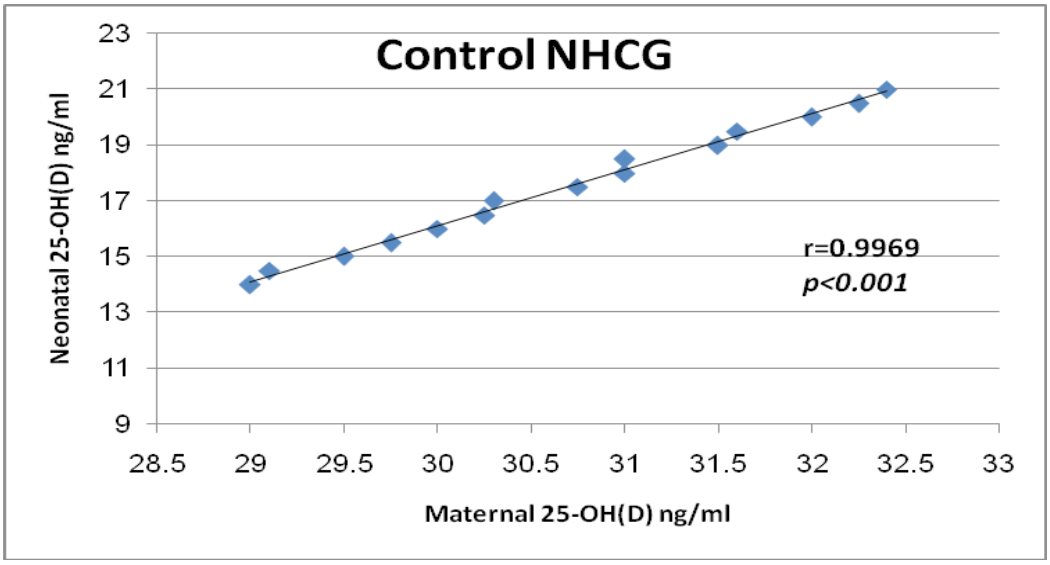

Fig. 2. correlation between maternal 25-OH (D) and corresponding neonates in NHCG.

It clarifies significant positive correlation between maternal 25-OH (D) and corresponding neonates in NHCG.

Discussion

The association between vitamin D status and anemia is of potentially great public health importance, It is increasingly appreciated that the potential benefits of vitamin D extend well beyond skeleton muscular maintenance, There is a growing evidence suggesting that 25OHD levels are associated withcardiovascular health, glycemic regulation, angiotensin regulated vascular responses, immune function, and cell differentiation (Santoro et al., 2015). Indeed, low 25OHD levels may increase the risk of heart disease, hypertension, stroke, and diabetes. Moreover, the immunomodulatory effects of vitamin D have been described in various diseases

(Riccio et al., 2015).As the final hydroxylation of vitamin D is dependent on iron, iron-deficient rats had lower concentrations of the active form of vitamin D. Diaz-Castro et al. also reported that bone metabolism was impaired despite normal 25(OH) D levels in iron-deficient rats. The main cause of decreased bone matrix formation was shown to be related to a decreased type I collagen amount. However, it is unclear whether severe IDA in humans would lead to the same phenomenon observed in animal studies (Diaz-Castro et al., 2012).

Iron deficiency anemia can result from inadequate iron intake, decreased iron absorption, increased iron demand, and increased iron loss (WHO, 2008).Iron-deficiency anemia accounts for 85% of all cases of anemia that are identified and is characterized by low mean cell volume (MCV). It is usually caused by nutritional deficiency or low iron stores resulting from previous pregnancy or previous heavy menstrual blood loss(Lambert and Beris, 2009).

With regard to anemia, there is a well-documented inverseassociation between 25OHD levels and the need for exogenouserythropoietin (EPO) among patients with anemia related torenal disease(Icardi et al., 2013). Insufficient production of EPO by the kidneys, and thus attenuated erythroid maturation in bone marrow is the main pathophysiologic mechanism believed to be responsiblefor anemia in chronic kidney disease (Nangaku et al., 2006).Erythroid precursors also requirehepcidin as a major mediator of iron absorption and utilization; hepcidin is pathologically upregulated by inflammatory cytokinesand results in a reduction in circulating iron levels (Babitt et al., 2010).

Activation of the vitamin D receptor in bone marrow (stromal and accessory cells) inhibits production of interleukin (IL)-1,IL-6, interferon-g, tumor necrosis factor-a, as well as otherproinflammatory cytokines, and upregulates production of

the anti-inflammatory cytokine, IL-10(Borges et al., 2011).These alterations incytokine expression have been shown to enhance erythroidproliferation and blunt hepcidin overproduction(Monlezume etal., 2015).

In this study we found that the level of vitamin D was significantly lower in pregnant women who had IDA in comparison to control group. This was consistent with a study done in south Korea showed a significant association between coexisting iron deficiency and vitamin D deficiency (Grindulis et al., 1986). Similar findings were also observed in recent Korean studies revealing that a coexisting vitamin D deficiency frequently accompanies iron deficiency (yoon et al., 2012), and this association might be due to suppressive effect of vitamin D on iron deficiency anemia (IDA) via Iron-Regulating Hormone Hepcidin which is a peptide hormone act as master regulator of iron homeostasis. Macrophages play a central role in iron recycling by engulfing senescent RBC. Iron receptor ferroportin binds iron and retain it in macrophages with the help of hepcidin. Recent studies suggest that vitamin D concentration are inversely proportional with hepcidin concentration and positively with hemoglobin and iron concentration (Dastidar et al., 2015).

The present study demonstrated a greater risk of vitamin D deficiency in pregnant women with IDA. The mean serum levels of vitamin D in IDAG was (19.8±2.9ng/nl) compared to the control non anemic pregnant women (30.75±1.12) where ($p<0.001$).There is a possibility that Vitamin D deficient individuals are malnourished and are having chronic inflammatory condition due to underlying chronic infection. Therefore Vitamin D administration can have a positive influence on the level of Hb rise. There are both in vivo and in vitro studies that show that 1, 25 hydroxyvitamin D reduces cytokine production. Therefore it reduces the inflammation and can have positive influence on Hb level rise(Pandyetal., 2015).

It has also been documented that hepcidin regulatesthe absorption, tissue distribution, and extracellular concentration of iron by suppressing the ferroportinmediatedexport of cellular iron (Bacchetta et al., 2014).Vitamin D is apotent regulator of the hepcidin-ferroportin axis. Therefore,vitamin D deficiency may affect the regulation ofhepcidin, which could accelerate the decrease in haemoglobinand increase the incidence of anaemia (Zughaier et al., 2014). Iron deficiency anaemia is the last end stage of progressionfrom normal iron status to frank deficiency(Madar et al., 2016).

In generally healthy adults, serum 25(OH) D concentrations <20 ng/mL were associated with lower hemoglobin concentrations and increased odds of anemia, particularly anemia of inflammation (Suh etal., 2016). High-dose vitamin D_3 supplementation reduced circulating hepcidin concentrations after one week among healthy adults; there were no changes in cytokine or ferritin concentrations. In critically ill adults (Ernst et al., 2016), treatment with high-dose vitamin D_3 resulted in increased hemoglobin concentrations over time; hepcidin concentrations did not change over time. These results provide preliminary evidence of a role for vitamin D in the regulation of iron metabolism. Larger clinical trials are warranted to fully evaluate the therapeutic efficacy of vitamin D in improving anemia (Smith et al., 2016).

Thomas et al., 2015 explained in his study that the significant indirect relation between vitamin D and hemoglobin was at least partly mediated by erythropoietin. They explained that this relation may have been mediated by a direct effect of calcitrol on erythroid precursors and the enhanced sensitivity of hematopoietic cells of erythropoietin, because calcitrol has been shown not only induce the proliferation of erythroid-derived human stem cells but also augment m RNA and protein expressions of the erythropoietin receptor in hematopietic tissues (Santoro et al., 2015).

The vitamin D-deficiency epidemic during pregnancy is caused by a lack of adequate sunlight exposure needed to synthesize vitamin D_3 in the skin, coupled with overall intakes that are too low to meet the increased demands of pregnancy (Hollis and Wagner, 2006). Previous studies of Bener et al., 2012 support these findings that vitamin D deficiency was more prevalent in Qatar and the population had less exposure to sun, although it is a sun-enriched population.

Vitamin D insufficiency has been associated with a number of adverse pregnancy outcomes, and has been recognized as a public health concern (Beneret al., 2013). .Maternal vitamin D deficiency in pregnancy is associated with low serum calcium in the newborn, with or without convulsions rickets and defective tooth enamel Effects on fetal growth have also been associated with maternal vitamin D deficiency. Population based studies have found lower birth weights and a higher risk of being small for gestational age and lower newborn bone mineral (Holick*et al.,* 2011).

We found a significant positive correlation in vitamin D levels between mothers and infants in both NHCG (r=0.9969, $p<0.05$*)* and IDAG(r= 0.3237, $p<0.001$). These results were similar to the findings of Mirzaeiet al., 2015.The vitamin D stores in the infant start with transplacental transfer of 25(OH)D in early pregnancy from mother to fetus. It is very obvious that maintaining optimum vitamin D nutrition during pregnancy is essential for prevention of hypovitaminosis D in the fetus and vitamin D deficiency at birth and in early infancy (Leeet al., 2015).

Positive significant correlations between maternal 25-OH (D) and their corresponding neonatal birth weight among both IDAG ((r=0.6334, $p<0.001$) and the controls (r= 0.5777, $p<0.0001$) were detected in the present study. This can be explained asvitamin D has a biologically plausible role in fetal growth. Vitamin D is important in glucose/insulin metabolism and homeostasis and so may play a role in glucose availability for transplacental transport and fetal usage (Suh et al 2016). As a regulator of calcium homeostasis and transport, calcitrol also can influence fetal growth directly through influences on skeletal muscle and bone development (Brodnaret al., 2010).

These findings provide evidence suggesting that vitamin D deficiency or insufficiency associated with anemia during pregnancy leads to adverse pregnancy outcome.Educational efforts are needed to increase compliance with iron and vitamin D supplementation guidelines. Further studies with larger sample size and cohort design are needed to determine the causality.

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تقييم فيتامين (د) في الامهات الحوامل المصابين بأنيميا نقص الحديد وأطفالهن حديثي الولادة

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انيميا نقص الحديد احد الامراض الاكثر شيوعا بين النساء الحوامل في جميع انحاء العالم.نقص فيتامين (د) اثناء الحمل قد يصاحبه بعض الاثار السلبية علي نمو الجنين .

صممت هذه الدراسة لتقييم العلاقة الممكنة بين انيميا نقص الحديد في الامهات الحوامل واطفالهن حديثي الولادة ونقص فيتامين (د), وتم قياس 25 هيدروكسي فيتامين (د) في مصل الام وجنينها حديث الولادة في عدد 25 سيدة حامل وتعاني من انيميا بسبب نقص الحديد ومقارنتها بالمجموعة الضابطة وعددها 15,وتم تقييم وزن جسم الاطفال حديثي الولادة وكذلك مقياس أبجار لتقييم الحالة الصحية لهم ومقارنتها في المجموعتين. وكشفت هذه الدراسة ان نقص 25 هيدروكسي فيتامين (د) كان احصائيا اكثر انتشارا في المجموعة التي تعاني من انيميا نقص الحديد بالمقارنة للمجموعة الضابطة.
وايضا يتناسب 25 هيدروكسي فيتامين (د) طرديا مع الوزن عند الولادة في المجموعتين وكانت العلاقة بين مستويات فيتامين (د) بين الامهات والرضع في كلا من المجوعتين ذات دلالة احصائية إيجابية.

وكشفت هذه الدراسة على ان السيدات الحوامل الاتي يعانين من انيميا نقص الحديد يصاحبهن نقص مستوى فيتامين (د) بالاضافة الى نقصه في مواليدهن وينعكس ذلك على وزنهم عند الولادة .