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RESEARCH ARTICLE

HYPOVITAMINOSIS D DELETERIOUSLY AFFECT PREGNANCY OUTCOME: A PROPOSED ROLE FOR DAILY VITAMIN D SUPPLEMENTATION TO IMPROVE OUTCOME.

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Keywords:-

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Abstract

Objectives: To estimate serum 25-hydroxy vitamin D (25OHD) levels in newly pregnant women and to evaluate its relation to development of gestational diabetes mellitus (GDM) and maternal and fetal outcome.

Patients & Methods: The study included 328 pregnant women, and at 6th week gestational age (GA), women's clinical and obstetric data were collected and blood samples were obtained for estimation of baseline blood glucose (BG) and serum 25OHD levels. Studied women were divided into two equal groups: Group A included pregnant women received supplemental vitamin D3 in a daily dose of 1000 IU oral capsule starting since 6th week GA till delivery. Group B included pregnant women who completed their pregnancy without vitamin D supplementation. All women underwent the 75g Oral Glucose Tolerance Test (75-OGTT) at the 20th, 28th and 36th week for detection of GDM. All women were followed up till delivery and maternal and neonatal outcome.

Results: Serum 25OHD levels were sufficient, insufficient and deficient in 42, 142 and 144 women, respectively. Forty-three women (13.1%) developed GDM and 62 women (18.9%) had emergency and 23 women had elective CS. Moreover, 48 neonates (14.6%) required NICU admission; 15 for respiratory-aid, 22 for phototherapy and 11 neonates for management of sepsis, but 4 neonates died. Women of group A showed significantly lower frequency of GDM with significantly lower BG levels, significantly lower frequency of CS especially emergency CS and significantly lower frequency of NICU admission.

Conclusion: Low serum 25OHD levels are a widespread problem among pregnant women and are associated with higher frequency of GDM, CS delivery especially emergency ones and NICU admission rate. Supplemental vitamin D therapy did well for reducing the frequencies of these events. Supplemental daily dose of 1000 IU appears appropriate and convenient as it was taken in the form of oral capsules.

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Introduction:-

Vitamin D is an important secosteroid hormone in skeletal and non-skeletal systems (Yoon, 2017). After absorption, vitamin D is bound to a binding protein which carries it in blood stream to the liver where vitamin D is hydroxylated into 25(OH) vitamin D (calcidiol), (Lapillonne, 2010) and then to the kidneys, where it is hydroxylated by CYP27B1 to 1,25 dihydroxy-vitamin D (calcitriol), which is the biologically active form of vitamin D (Cho et al., 2013).

Vitamin D receptors (VDR) are present in many non-skeletal tissues, so vitamin D via the binding to VDR can produce a number of desired biological effects via different mechanisms and, therefore, contributes to the improvement of human health (Teegarden & Donkin, 2009).

However, accumulating evidence suggests that the metabolic pathways of vitamin D may play a key role in the development of gynecological/obstetric diseases (Colonese et al., 2015), such as polycystic ovary syndrome (Velija-Ašimi, 2014), endometriosis (Sayegh et al., 2014), and ovarian and even breast cancer (Goodwin et al., 2009). Moreover, the maternal-fetal unit is under the influence of vitamin D, as a breakdown in its homeostasis may underlie infertility, preeclampsia, and gestational diabetes mellitus (Colonese et al., 2015).

Gestational diabetes mellitus (GDM) arises in women developed insufficient β -cell compensation for the insulin resistance of late pregnancy (Retnakaran et al., 2016). GDM is characterized by rising incidence, fostered by the worldwide increase of pathological nutritional status from young age (Triunfo et al., 2017).

The mechanisms underlying both normal antepartum β -cell adaptation and its aberrancy in GDM are unclear (Retnakaran et al., 2016). However, high maternal blood glucose (BG) levels during pregnancy induces adverse intrauterine environment, which has a negative impact on health outcomes for both the mother and the offspring (Silva-Zolezzi et al., 2017). On the other side, maternal vitamin D status is independently associated with markers of physiological and pathological growth in term infants (Gernand et al., 2012).

According to that previously documented by Wahlberg et al., (2016), each of vitamin D deficiency and GDM has been associated with increased risk of adverse perinatal outcomes, but the consequences of simultaneous presence of both conditions during pregnancy needs to be evaluated; thus, the current study aimed to estimate serum 25-hydroxy vitamin D (25OHD) levels in newly pregnant women and to evaluate its relation to development of GDM and maternal and fetal outcome.

Setting:-

Faculty of Medicine and University Hospital, Benha, Egypt

Design:-

Clinical prospective observational study

Patients & Methods:-

The present study was started since Jan 2015 to July 2017. The study protocol was approved by the Local Ethical Committee and only women signed a written fully informed consent were included in the study. All pregnant women who attended the Antenatal Outpatient Clinic, at Benha University hospital for assurance of diagnosis of being pregnant were eligible for study inclusion. At 6th week gestational age (GA), women's demographic and anthropometric data and previous clinical and obstetric data were collected. Body mass index (BMI) was calculated using the formula: weight (kg)/ height (m²) and patients were classified according to BMI using the World Health Organization ranges as underweight: BMI<18.5 kg/m², normal weight: BMI=18.5-24.9 kg/m², overweight: BMI=25-29.9 kg/m² and obese: BMI= \geq 30 kg/m² (14).

At meantime, a random blood samples were obtained under complete aseptic conditions from the antecubital vein and divided into two parts:

1. The first part was put in a tube containing sodium fluoride (2 mg sodium fluoride/ ml blood) to prevent glycolysis. Plasma was separated by centrifugation and used for estimation of fasting blood glucose (FBG) by glucose oxidase method (Tinder, 1969).
2. The second part was put in a plane container and left to clot at room temperature for 30 minutes before centrifugation for 20 minutes at 1,000g. Freshly prepared serum was stored at -20°C till estimation of fasting serum 25-OHD levels using an ELISA kit (Cayman Chemical, Ann Arbor, MI, USA) (Andersen et al., 1993).

Vitamin D sufficiency status was defined according to 25-OHD concentration as follows: ≥ 75 nmol/L sufficient level, 50-75 nmol/L insufficient level and < 50 nmol/L deficient level. Vitamin D deficiency was categorized as mild, moderate and severe if 25-OHD concentration was 25-50 nmol/L, 12.5-25 nmol/L and < 12.5 nmol/L, respectively (Stroud et al., 2008).

Women with current DM, history of previous GDM or obesity-inducing endocrinopathy, evident manifestations of hypo-parathyroidism, thyrotoxicosis, renal or hepatic diseases and women lost during the course of pregnancy were excluded from the study.

After fulfilling the inclusion and exclusion criteria, enrolled women were randomly divided using sealed envelopes, prepared by an assistant blinded about the study plan, target for grouping and results of laboratory investigation, into two equal groups:

- **Group A:** included pregnant women assigned to received supplemental vitamin D3 according to Grant et al., (2014) in a daily oral dose of 1000 IU softgels to be taken with meal (Sunvite High Potency Vitamin D3 1000 IU; Puritan's Pride, Inc., Oakdale, NY, USA). Vitamin D supplementation started since 6th week GA till delivery.
- **Group B:** included pregnant women who will complete their pregnancy without vitamin D supplementation.

All enrolled women were asked to fast and attend the antenatal care unit at the 20th, 28th and 36th week GA. At time of each visit, all women underwent the 75g Oral Glucose Tolerance Test (75-OGTT) which entails obtaining three blood samples an overnight fasting blood sample and then each woman was given an oral snack containing 75 gm glucose and another two blood samples were obtained at 1-hr and 2-hr postprandial (PP) for estimation of blood glucose. Women were categorized as having gestational diabetes mellitus (GDM) or not according to the criteria of the International Association of Diabetes and Pregnancy Groups (IADPSG, 2010) for abnormal OGTT, as follows: FBG ≥ 92 mg/dl, 1-h BG ≥ 180 mg/dl and 2-h BG ≥ 153 mg/dl. All women were followed up till delivery and maternal and neonatal outcome were reported.

Statistical analysis:-

Obtained data were presented as mean \pm SD, ranges, numbers and ratios. Results were analyzed using One-way ANOVA with post-hoc Tukey HSD test, and Chi-square test (X2 test). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value < 0.05 was considered statistically significant.

Results:-

Throughout the duration of the study, 361 women were eligible for evaluation, 33 women were excluded and 328 women were included in the study (Fig. 1). Patients' demographic and clinical data and laboratory findings determined at time of 1st antenatal visit showed non-significant ($p > 0.05$) difference between both groups as shown in table 1.

Table (1):- Patients' data determined at 1st antenatal visit (6th week GA)

Data	Group A (n=164)	Group B (n=164)	P value	
Age (years)	28.6 \pm 3.2	28.3 \pm 2.9	0.379	
Weight (kg)	84.8 \pm 11	86.8 \pm 12.2	0.118	
Height (cm)	168.7 \pm 3.3	169.2 \pm 4.3	0.213	
Body mass index (kg/m ²)	29.8 \pm 4.1	30.4 \pm 4.7	0.259	
Gravidity	2.4 \pm 1	2.6 \pm 1.1	0.051	
Parity	1.2 \pm 0.9	1.4 \pm 1.1	0.128	
Laboratory data	Fasting blood glucose	81.6 \pm 11.2	80.4 \pm 10.1	0.302
	Serum 25-OHD	48.7 \pm 22.8	50.8 \pm 21.2	0.393

Data are presented as mean \pm SD & numbers; percentages are in parenthesis; 25-OHD: 25-hydroxy vitamin D; $p > 0.05$: indicates non-significant difference

Only 42 women (12.8%) out of the total study population, had sufficient serum 25-OHD, 142 women (43.3%) had insufficient serum level and 144 women (43.9%) had deficient serum levels. Out of women had deficient 25-OHD serum level, 77 women (23.5%) had mild deficiency, 49 women (14.9%) had moderate deficiency and 18 women (5.5%) had severe deficiency (Fig. 2). Patients' distribution according to extent of 25-OHD sufficiency showed non-

significant ($p > 0.05$) difference between studied groups among the main categories and categories of deficiency. Moreover, the differences between estimated levels showed non-significant ($p > 0.05$) difference between patients of both groups (Table 2, Fig. 3).

Table (2):- Patients' distribution according to serum 25-OHD estimated the 6th week GA

Data		Group A (n=164)	Group B (n=164)	P value	
Frequency	Sufficient	19 (11.6%)	23 (14%)	0.514	
	Insufficient	68 (41.5%)	74 (45.1%)		
	Deficient	77 (46.9%)	67 (40.9%)		
	Deficiency	Mild	36 (22%)	41 (25%)	0.473
		Moderate	31 (18.9%)	18 (11%)	
Severe		10 (6%)	8 (4.9%)		
Levels (ng/ml)	Sufficient	79.7±2.9	78.3±2.4	0.113	
	Insufficient	65±7.5	62.9±5.8	0.069	
	Deficient	26.6±9.6	27.8±10.2	0.465	
	Deficient	Mild	35.7±4	34.8±5.7	0.439
		Moderate	21.1±2.3	19.7±2.8	0.063
Severe		11.1±0.9	10.6±1.1	0.313	

Data are presented as mean±SD & numbers; percentages are in parenthesis; $p > 0.05$: indicates non-significant difference

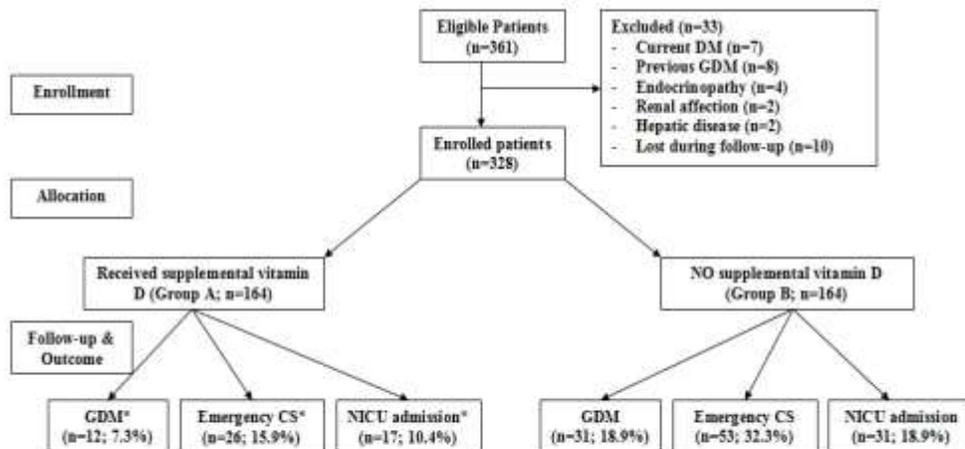


Fig. (1): Flow chart of the study (*: Significantly lower)

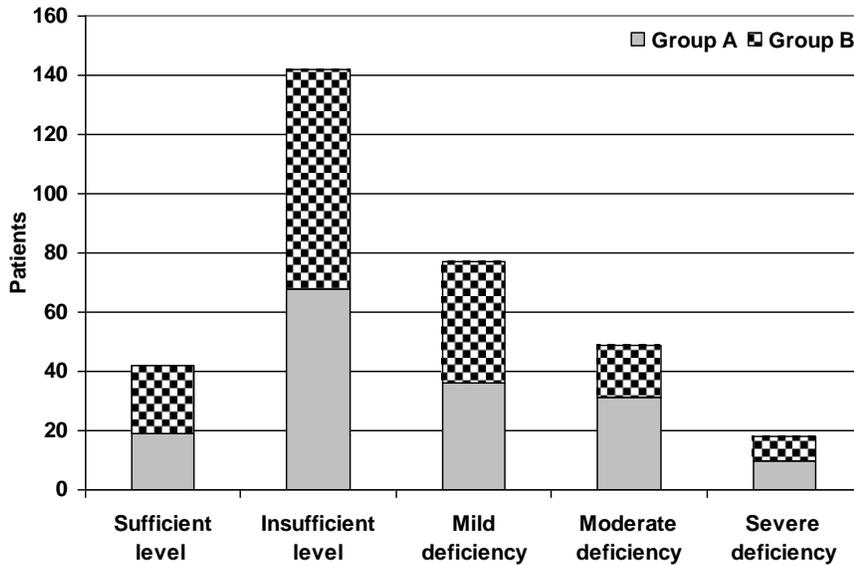


Fig. (2): Patients' distribution among sufficiency grades of vitamin D as estimated at 1st antenatal visit

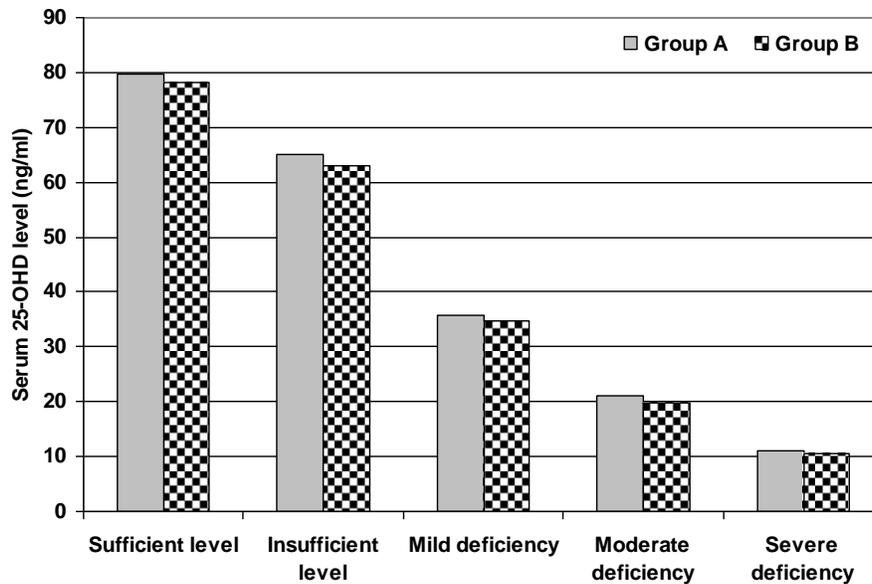


Fig. (3): Mean serum 25-OHD level estimated in studied women categorized according to vitamin D sufficiency grade

Throughout the observation period, 43 women developed gestational diabetes mellitus (GDM) for a frequency of 13.1%. Only, 12 of women received supplemental vitamin D therapy (Group A), while 31 of women did not receive supplemental vitamin D therapy (Group B) developed GDM with significantly ($p=0.002$) lower frequency of GDM among women of group A than group B. Time course development showed non-significantly ($p>0.05$) lower frequency of women developed GDM among women of group A compared to women of group B at 20th and 36th week GA, while the frequency was significantly ($p=0.004$) lower at 28th week GA (Fig. 4). Concerning blood glucose levels estimated during 75-OGTT, at the 20th week GA, FBG and 2-hr PP blood glucose levels were non-significantly ($p>0.05$) lower, while 1-hr PP blood glucose levels were significantly ($p=0.046$) lower in women of group A than women of group B. At both 28th and 36th week GA, all of the three blood samples showed significantly lower blood glucose levels in women of group A compared to women of group B (Table 3).

Table (3):- Patients' distribution according to the results of 75-OGTT performed throughout the observation period

Data			Group A (n=164)	Group B (n=164)	P value
Frequency of patients developed GDM throughout observation period	At 20 th week GA	Yes	4 (2.4%)	5 (3%)	0.735
		No	160 (97.6%)	159 (97%)	
	At 28 th week GA	Yes	6 (3.7%)	20 (12.2%)	0.004
		No	154 (93.9%)	139 (84.8%)	
	At 36 th week GA	Yes	2 (1.2%)	6 (3.7%)	0.113
		No	152 (92.7%)	133 (81.1%)	
	Total	Yes	12 (7.3%)	31 (18.9%)	0.002
		No	152 (92.7%)	133 (81.1%)	
Results of 75-OGTT determined throughout observation period	20 th week levels	FBG	82.8±7.7	84.7±9.4	0.064
		1-hr PP	160.6±14.3	163.2±8.1	0.046
		2-hr PP	122.7±7.8	123.4±7.1	0.057
	28 th week levels	FBG	84.4±10.4	88.9±13.9	0.002
		1-hr PP	161.6±14.6	168.4±22.8	0.002
		2-hr PP	123.1±10.4	127.1±15.9	0.010
	36 th week levels	FBG	86.1±11.8	91.1±13.9	0.001
		1-hr PP	165.6±14.6	170.6±21.9	0.012
		2-hr PP	124.1±11.6	128.4±17.1	0.009

Data are presented as mean±SD & numbers; percentages are in parenthesis; GDM: Gestational diabetes mellitus, GA: Gestational age; 75-OGTT: 75 gm oral glucose tolerance test; FBG: Fasting blood glucose; PP: Postprandial blood glucose; p<0.05: indicates significant difference; p>0.05: indicates non-significant difference

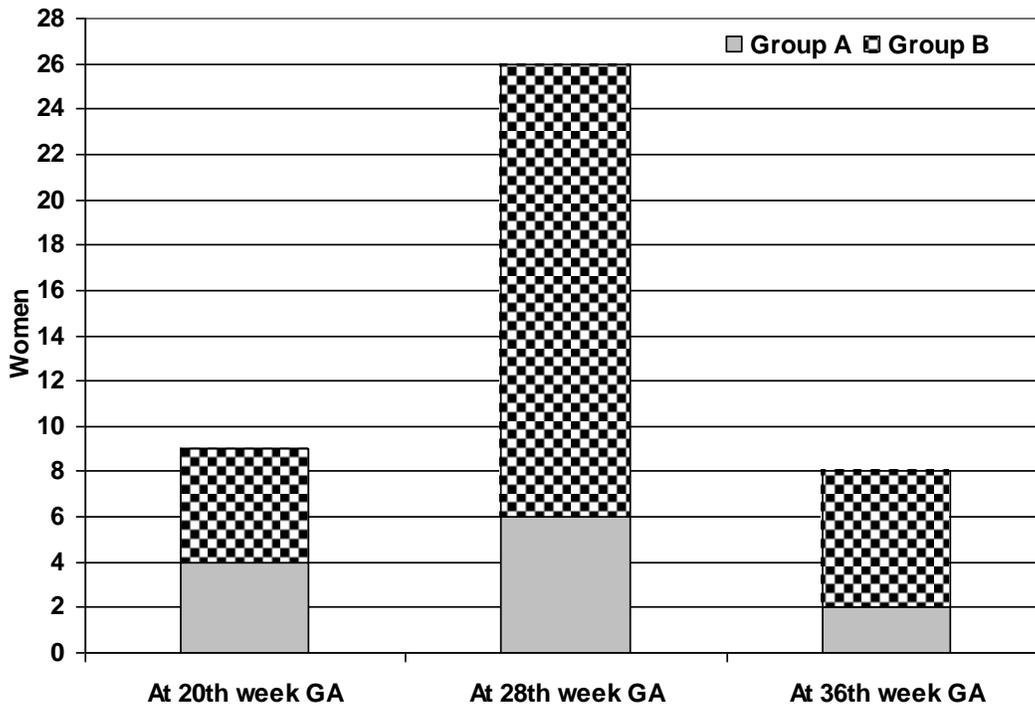


Fig. (4): Time course development of GDM among studied women through out observation period

Eighty-five women (25.9%) had cesarean section (CS); 34 in group A and 51 in group B with significantly ($p=0.032$) lower frequency of CS among women of group A than in group B. Distribution of women had CS showed significance difference between women of both groups categorized according to extent of sufficiency of vitamin D levels ($p=0.042$) and according to development of GDM ($p=0.035$) (Fig. 5). Sixty-two women (18.9%) had emergency CS; 21 in group A and 41 in group B with significantly ($p=0.041$) lower frequency of emergency CS among women of group A than in group B. Distribution of women had emergency CS showed significance difference between women of both groups categorized according to extent of sufficiency of vitamin D levels ($p=0.047$) and non-significantly ($p=0.097$) according to development of GDM (Table 4).

Table (4):- Maternal outcome of studied women of both groups

Outcome		Total (n=328)	Group A (n=164)	Group B (n=164)	P value
Mode of delivery	Normal vaginal delivery	243 (74.1%)	130 (79.3%)	113 (68.9%)	0.032
	CS	85 (25.9%)	34 (20.7%)	51 (31.1%)	
Frequency of CS according to estimated levels of	Serum 25-OHD	Sufficient (n=42)	2 (5.9%)	4 (7.8%)	0.042
		Insufficient (n=142)	20 (58.8%)	16 (31.4%)	
	BG	Deficient (n=144)	43 (50.6%)	12 (35.3%)	0.035
		Normal (n=285)	68 (80%)	31 (91.2%)	
Type of CS	Elective	23 (27.1%)	13 (38.2%)	10 (19.6%)	0.041
	Emergency	62 (72.9%)	21 (61.8%)	41 (80.4%)	
Frequency of emergency CS according to estimated levels of	Serum 25-OHD	Sufficient (n=10)	1 (4.8%)	2 (4.9%)	0.047
		Insufficient (n=46)	26 (41.9%)	14 (34.1%)	
	BG	Deficient (n=53)	33 (53.3%)	8 (38.1%)	0.097
		Normal (n=88)	45 (72.6%)	18 (85.7%)	
		GDM (n=21)	3 (14.3%)	14 (34.1%)	

Data are presented as numbers & mean±SD; percentages are in parenthesis; CS: Cesarean section; 25-OHD: 25-hydroxy vitamin D; BG: Blood glucose; GDM: Gestational diabetes mellitus; $p<0.05$: indicates significant difference; $p>0.05$: indicates non-significant difference

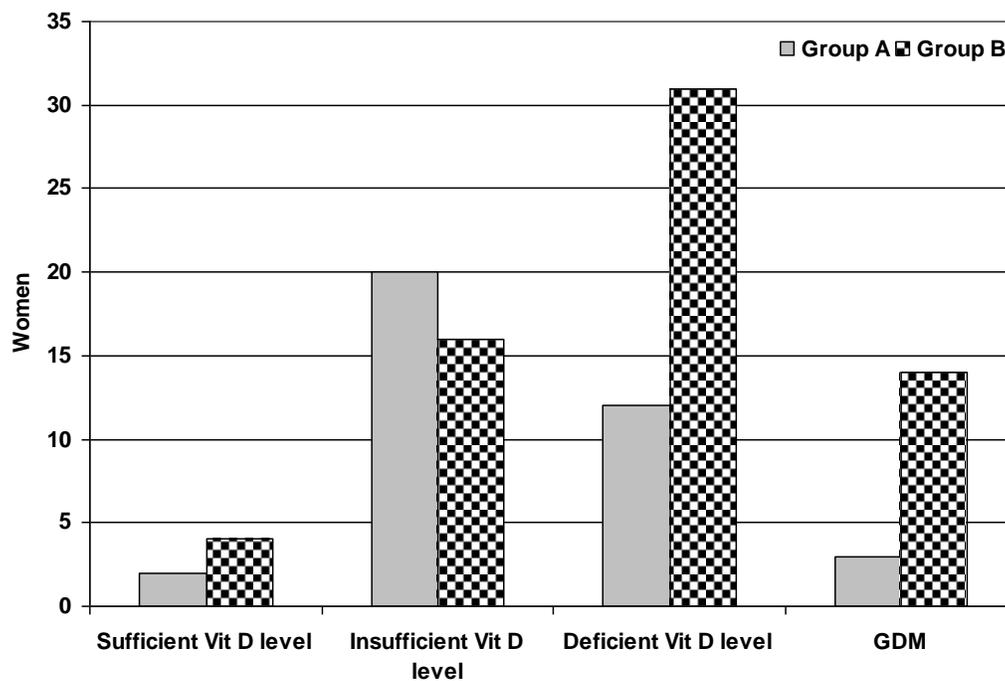


Fig. (5): Frequency of women had CS among studied women categorized according to vitamin D grades and development of GDM

Mean APGAR score determined at 1-min and 5-min was significantly higher in neonates of group A than those of group B. Differentially according to the extent of vitamin D sufficiency, mean APGAR score was significantly higher in neonates of group A than in neonates of group B. Mean APGAR score of women categorized according to estimated blood glucose levels was significantly higher in neonates of group A than in group B. Forty-eight neonates (14.6%) required NICU admission with significantly ($p=0.029$) lower frequency of NICU admission among neonates of group A compared to group B. Fifteen neonates required respiratory-aid and 22 required phototherapy management of hyperbilirubinemia with non-significantly higher frequencies among neonates of group B. Eleven neonates were NICU admitted for management of sepsis with significantly higher frequency among neonates of group B. Unfortunately, three neonates of group B and one of group A died with non-significant difference in favor of group A (Table 5).

Table (5):- Neonatal outcome of studied women of both groups

Outcome			Group A (n=164)	Group B (n=164)	P value	
APGAR-1	according to estimated levels of	Serum 25-OHD	Sufficient (n=42)	7.9±1	7.1±1.2	0.070
			Insufficient (n=142)	6.5±0.9	6.3±0.8	0.311
			Deficient (n=144)	6.2±0.8	5.8±0.8	0.001
		BG	Normal (n=285)	6.6±1	6.4±1	0.005
			GDM (n=43)	6.3±0.7	5.5±0.8	0.003
APGAR-5	according to estimated levels of	Serum 25-OHD	Sufficient (n=42)	8.9±0.8	8±1.3	0.005
			Insufficient (n=142)	8.7±0.8	7.4±1.4	0.001
			Deficient (n=144)	8.6±0.6	7.2±1.2	0.001
		BG	Normal (n=285)	7.1±0.8	6.8±0.7	0.271
			GDM (n=43)	8.8±0.5	7.5±1.4	0.001
NICU admission	Yes	17 (10.4%)	31 (18.9%)	0.029		
	No	147 (89.6%)	133 (81.1%)			
Indication for NICU admission	Ventilation	8 (47.1%)	10 (32.3%)	0.082		
	Phototherapy	7 (41.2%)	12 (38.7%)	0.727		
	Sepsis	2 (11.8%)	9 (29%)	0.037		
NICU Mortality rate			1 (5.9%)	3 (9.7%)	0.649	

Data are presented as numbers & mean±SD; percentages are in parenthesis; 25-OHD: 25-hydroxy vitamin D; BG: Blood glucose; GDM: Gestational diabetes mellitus; NICU: Neonatal ICU; $p<0.05$: indicates significant difference; $p>0.05$: indicates non-significant difference

Discussion:-

Estimated serum 25OHD levels were insufficient in 142 women (43.3%) and deficient in 144 women (43.9%), while only 42 women had sufficient serum levels. This finding goes in hand with Loy et al., (2015) who reported a frequency of 25ODH inadequacy in 41.3% of their series of pregnant women. Thereafter, O'Callaghan-Gordo et al., (2017) documented that the prevalence of vitamin D deficiency is globally high. Both of Naseh et al. (2017) and Kilicaslan et al., (2017) reported that out of a sample population of pregnant women, no mother had sufficient vitamin D level, while 27% and 53% had vitamin D deficiency and 73% and 47% had vitamin D insufficiency. Furthermore, Wierzejska et al., (2017) documented that despite of higher maternal and umbilical cord blood concentrations of vitamin D in summer than in winter, only 16% of the pregnant women reached the optimal vitamin D concentration during summer.

Throughout the observation period, 43 women (13.1%) developed GDM and 109 women (33.2%) had CS; 62 women (24.1%) had emergency and 23 women had elective CS. Moreover, 48 neonates (14.6%) required NICU admission; 15 for respiratory-aid, 22 for phototherapy management and 11 neonates for management of sepsis, but unfortunately, 4 neonates died.

These data are in accordance with Lacroix et al., (2014) who reported that lower first trimester 25OHD levels were associated with higher risk of developing GDM and Jafarzadeh et al., (2015) who found a significant and inverse relationship between serum levels of 25OHD in the second trimester with insulin and 2-hr BG on 75-OGTT at 24-28 weeks GA. Thereafter, Lu et al., (2016) out of a meta-analysis included 20 observational studies containing 16,515 pregnant women documented that maternal vitamin D insufficiency is associated with increased risk of GDM. Also,

Dodds et al., (2016) in a case-control study supported the inverse association of vitamin D status with GDM risk. Moreover, De-Regil et al., (2016) detected vitamin D adequacy, inadequacy and deficiency in 23, 39.5 and 37.5%, respectively and found 7.5% of pregnant women developed preeclampsia, 6.5% developed GDM. Also, Al-Shaikh et al., (2016) found 86.4 % of their series of pregnant women had vitamin D deficiency and that GDM was the commonest complication which was detected in 11.1 %, while 24.5% of these women had history of miscarriage. Recently, Triunfo et al., (2017) reported that in pregnant women, lower 25OHD concentrations showed an inverse association with maternal glycaemia and increased risk of GDM.

The reported neonatal sequale of vitamin D status is in accordance with Weinert et al., (2016) who found newborns of women with vitamin D deficiency had higher incidences of ICU admission and of hypoglycemia. Ajmani et al., (2016) found that 9.5% of women with vitamin D deficiency delivered low-birth weight babies, 6% delivered premature babies and 8% of babies had APGAR score <7 at 5 min, and 6% of babies were admitted in NICU. Bartáková et al., (2017) detected higher risk for adverse perinatal outcomes in women with low vitamin D levels.

Pregnant women included in group A, who had received supplemental vitamin D therapy since 6th week GA till delivery in a daily dose of 1000 IU, showed significantly lower frequency of developing GDM with significantly lower blood glucose levels throughout the observation period in comparison to pregnant women who did not receive supplemental vitamin D therapy (Group B). Moreover, supplemental vitamin D therapy improved maternal and fetal outcome of women of group A that was manifested as significant reduction for the need for CS especially emergency CS with significantly lower frequency of newborns that required NICU admission. Interestingly, newborns of women of group A showed significantly lower frequency of NICU admission for septic indication, a finding indicating improvement of immunity of both the mother and the fetus that reflected as decreased frequency of neonatal sepsis.

In line with the use of supplemental vitamin D during pregnancy, Wierzejska et al., (2017) documented that despite improvement of vitamin D levels in summer, it does not guarantee that supplementation throughout the whole year is inessential. Moreover, Kiely et al., (2017) reported that estimated vitamin D metabolites in umbilical cord blood emphasize the high risk of very low vitamin D status in infants born to un-supplemented mothers.

The provided daily dose of supplemental vitamin D goes in hand with that previously documented in literature; where Cooper et al., (2016) found supplementation of women with cholecalciferol 1000 IU/day during pregnancy is sufficient to ensure that most pregnant women are vitamin D replete, and it is safe. Ceccaldi et al., (2017) documented that despite national guidelines on vitamin D supplementation, the rates are currently insufficient and the recommended 100,000 IU single dose helps to limit deficiency in newborns, but it fails to cover infant's needs for optimal status. Yilmaz et al., (2017) who documented that in order to be able to prevent neonatal vitamin D deficiency, 1200 IU/day vitamin D was supplemented to mothers from the 12th gestational week to 6th month of the birth,

In support of the fetal benefit of maternal vitamin D supplementation, De-Regil et al., (2016) reported that data from three trials involving 477 women suggest that vitamin D supplementation during pregnancy reduces the risk preterm birth and increases infant length and head circumference at birth compared to no intervention or placebo and Kilicaslan et al., (2017) found that height; head circumference and chest circumference of newborns born to mothers who had received vitamin D support were significantly higher compared to non-receivers.

Conclusion:-

Low serum 25OHD levels are a widespread problem among pregnant women and are associated with higher frequency of GDM, CS delivery especially emergency ones and NICU admission rate. Supplemental vitamin D therapy did well for reducing the frequencies of these events. Supplemental daily dose of 1000 IU appears appropriate and convenient as it was taken in the form of oral capsules. However, wider scale studies are recommended to assure the benefit of vitamin D supplementation for other pregnancy-induced complications.

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