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Prevalence of hypocalcemia in asymptomatic pregnant females in Upper Egypt

Asmaa Hussein Abdel Aty [a], *Mohamed Abdel Fattah Youssef* [b] *and Yasser Khamis Mohamed* [a]

[a] Obstetrics and Gynecology department, Faculty of Medicine, Beni-Suef University, Egypt

[b] Obstetrics and Gynecology department, Faculty of Medicine, Cairo University, Egypt

Abstract:

The goal of this study is to investigate the levels of serum calcium in asymptomatic pregnant women and measuring the prevalence of hypocalcaemia. Healthy pregnant women (n=500) were enrolled consecutively, with singleton pregnancy, in first trimester with the mean gestational age (9.5 ±1) weeks of gestation. Serum Total and Ionized calcium were measured to all women in the study. The prevalence of hypocalcaemia was measured. Nearly two thirds of women (337) had hypocalcaemia (67.4%), Only 163 had normal calcium levels" serum calcium level of 8.6 mg/dL or above". The prevalence of hypocalcaemia was more in young aged women as about two-thirds (64.8%) were in the age group 20 to less than 30 years, with mean age 23.9 ±4.6 years. Also the prevalence of hypocalcaemia was high in parity less than 2, with statistically significant p-value (0.034). No determinants (education, dietary intake of Ca^{+2}, weight, height, BMI, and Hb levels) found in our study to be in correlation with the high incidence of hypocalcaemia.

Keywords: Prevalence; hypocalcaemia; pregnant.

1. Introduction:

Calcium is the most abundant mineral in the human body. It has several main functions in the body. It binds to proteins resulting in change of the electrical charges on the protein chain, causing the protein's tertiary structure to change. Good examples are many of the clotting factors within the plasma, which are not functioning if Ca^{+2} ions are not present, but become completely functional on adding the correct concentration of Ca^{+2} salts. The voltage gated sodium ion channels in the cell membranes of nerves& muscle are in particular sensitive to the Ca^{+2} ion concentrations in the plasma [1]. Also calcium is an important cofactor for hormonal secretion in

endocrine organs. The total concentration of serum Ca^{+2} should be normally kept within the very narrow range of (8.5-10.5) mg/dL (2.12- 2.62 mmol/L) for optimal and normal functioning of these processes [2]. Over 99 % of total body calcium in bones and teeth is found as calcium hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$), it provides strength to hard tissue. Bone can act as a reservoir for and supply of calcium for these metabolic processes through the process of bone remodeling [3]**.** Although >99% of the whole body calcium is found in bone, calcium is a critical cation in both the extracellular and intracellular spaces. About 1% of the calcium in the skeleton is freely exchangeable with calcium in the extracellular fluid compartment. Serum calcium concentration is held in a very narrow range in both spaces [4]. Bone remodeling is responsible for maintenance of serum calcium levels. Calcium homeostasis includes maintaining both albumin bound and free ionic Ca^{+2} in intracellular and extracellular compartments [5]. Regulation of calcium and phosphate metabolism depends on several important hormones, chiefly parathyroid hormone (PTH), 1, $25(OH)_2$ D_3 (calcitrol) , and fibroblast growth factor-23 as well as molecular sensors for calcium including the so-called calcium-sensing receptor[6]. The main function of PTH is controlling Ca^{+2} concentration in the extracellular fluid using membrane receptor that serves as a Ca^{+2} sensor. PTH release is enhanced when Ca^{+2} level is reduced. Additionally, Ca^{+2} regulate the activity of PTH gene [7]. The major action of the activated form of vitamin D is to increase the absorption of calcium from the intestine. Calcitriol also sensitizes bone to the resorptive actions of PTH. There is also recent evidence that vitamin D controls parathyroid gland growth and suppresses the synthesis and secretion of PTH. The formation of 1, 25-(OH) 2D3 in the kidneys is regulated in feedback fashion by plasma calcium levels [8]. Calcitonin is produced by the Para follicular or C cells of the thyroid gland. It is functionally an antagonist to PTH and Vitamin D3.

It lowers blood Ca^{+2} levels in two ways:

Major effect: Inhibits osteoclast activity in bones, which break down the bone

Minor effect: Inhibits renal tubular cell reabsorption of Ca and phosphate, allowing them to be excreted in the urine [9]. There are biological limits to a pregnant woman's capacity to promote Ca^{+2} absorption, and if she doesn't consume sufficient amounts of dietary Ca^{+2}, she may be at high risk for gestational complications. Dietary deficiencies of calcium during pregnancy have been implicated in preeclampsia, eclampsia, preterm birth, intrauterine growth retardation or long-term

morbidities, such as excessive bone loss [10].

2. Patients and Methods :

This was a cross-sectional study performed in the department of Obstetrics and Gynecology in El-Fayoum general hospital at the period from June 2018 to June 2019 involving 500 women. The nature of the study was explained for each patient before enrollment in the study and written consent for inclusion in it was obtained.

Inclusion criteria:

Women were less than 40 years old and more than 20 years old. All cases are diagnosed to be pregnant in the first trimester with singleton pregnancy. No history of calcium supplementation before start of study. No history of chronic medical disease or receiving therapies known to interfere with Ca^{+2}metabolism as anticonvulsants drugs, corticosteroids, thyroxin, and heparin.

Exclusion criteria:

Twins pregnancy and Grand multiparas are not enrolled in the study cases. History of chronic diseases (DM, thyroid, renal disorders) also should be excluded.

- **All the participants were subjected to:**

At the first antenatal visits;

1) **History taking :**

A detailed family and medical history were taken. (Age, Parity, History of chronic diseases, History of drug intake, History of special habits as alcohol consumption or smoking).

2) **Examination:**

Thorough clinical examination was done in all the subjects "Body Mass Index (BMI), Systolic and diastolic blood pressure was carefully recorded.

3) **Ultrasonographic examination:**

Done to detect number of fetuses, Viability, Gestational age and Congenital anomalies.

In this study we will measure: Serum Total and Ionized calcium to women in first trimester.

Blood was taken from the ante cubital vein using a sterile needle and syringe. Blood was collected at 7 am in the morning after overnight fasting. Blood samples were allowed to clot and then centrifuged at 3000 revolutions per minute for 10 minutes. Serum calcium level was measured by Colorimetric method. Whenever possible, the analysis was done immediately. When there was a delay, the samples were stored at -20 Celsius till further analysis. Serum calcium was estimated by the O- Cresol Phthalene Complexone method with Erba model Chem 5 plus.

Statistical methodology

Data was expressed as Mean ± Standard Deviation. Data analysis was done by SPSS version 20. Student t- test and Chi-square tests was used to compare the continuous and categorical data

respectively. Pearson correlation coefficient was calculated for serum calcium concentration and p-value of < 0.05 was considered as statistically significant.

3. Results:

Our study enrolled 500 asymptomatic pregnant women, who met inclusion criteria. All women in our study were pregnant in first trimester with the mean gestational age (9.5 ±1)weeks of gestation. The socio-demographic characteristics of pregnant women there are about two-thirds (64.8%) of them were in the age group 20 to less than 30 years, with mean age 23.9 ±4.6 years. More than one-third of the women were illiterate, while only 3.4% of them had university education. The great majority (95.2%) were housewives. More than one-quarter (27.6%) live in urban areas, while (68.2%) of them live in rural areas as shown in Table (1).

During studying the relation between blood calcium and various socio-demographic characteristics of pregnant women in our study sample we found, None of these characteristics could show to have any statistically significant differences with blood calcium, ($p<0.05$) as illustrated in Table (1)**.**

Table (1): Distribution of the patient sample by their Socio-demographic characteristics (n=500) and Relation between maternal serum calcium and their Socio-demographic characteristics.

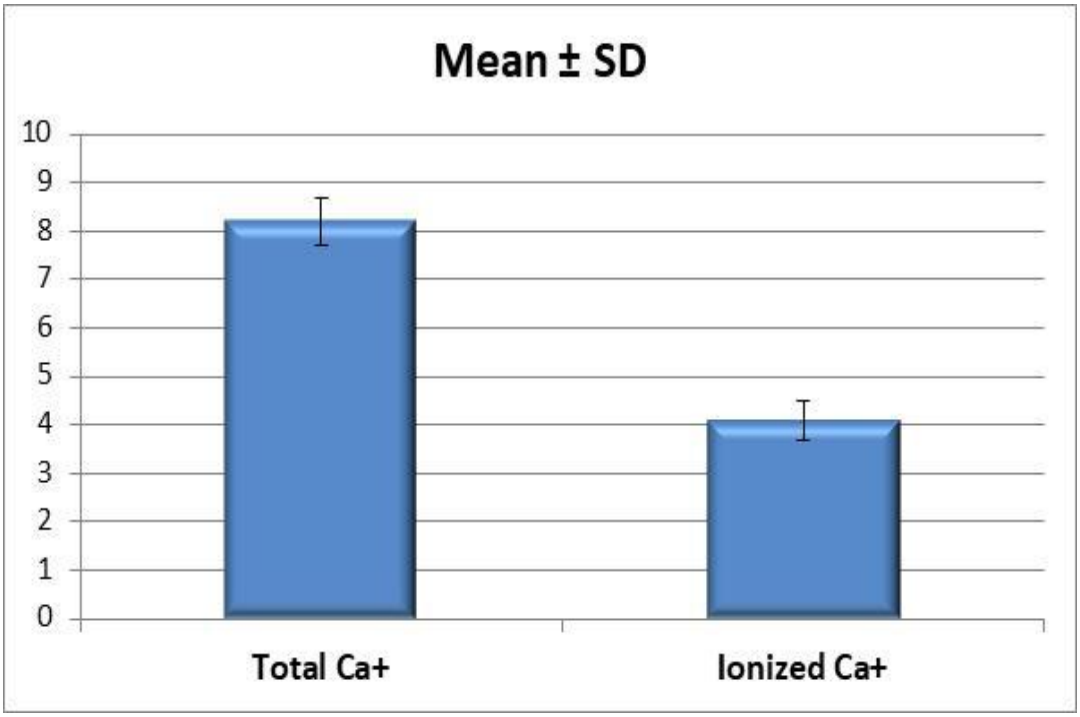
	Frequency	**Percent**	**Blood Ca(mg/dl) Mean ±SD**	**P-value**
Age (years)				
<20	84	16.7		
20-25	326	64.8		
25-30	93	18.5		
Education :				
Illiterate	179	35.6	8.9±1.7	
Read/write	24	4.8	9.7±1.5	0.41
Basic	125	24.9	8.8±1.2	
Secondary	142	28.3	8.8±1.7	
Intermediate	14	3.0	9.2±1.5	
University	17	3.4		

Job status:				
Housewife	476	95.2	8.9±1.5	0.36
Working	24	4.8	9.3±1.9	
Residence :				
Rural	341	68.2	8.9±1.5	
Semi-urban	20	4.2	}8.9±1.6	0.73
Urban	139	27.6		

Total and ionized calcium levels were measured and we noticed that:

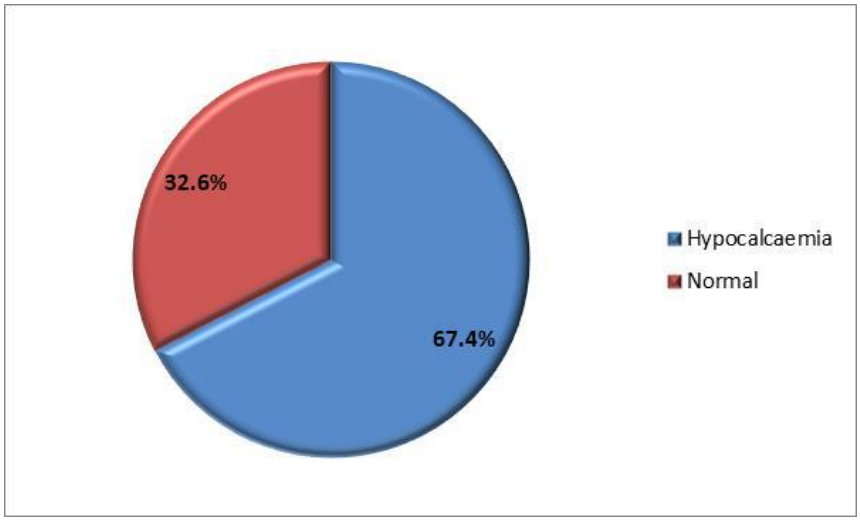
The mean serum calcium level was noted to be 8.2 ±0.5mg/dl (ranging from 7.7mg/dl to 8.7mg/dl). Mean serum ionized calcium level was noted to be 4.1 ± 0.4 (ranging from 3.7 mg/dl to 4.5mg/dl) as shown in **Figure1**.

Figure (1): Mean and SD of total and ionized calcium



The prevalence of hypocalcaemia was measured. It was found to be very high. Nearly two thirds of women had hypocalcaemia (67.4%). Those with hypocalcaemia ”serum calcium 8.5 mg/dL or below” were 337 woman while only 163 had normal calcium levels “those with serum calcium level of 8.6 mg/dL or above” as described in **figure 2**.

Figure (2): Prevalence of hypocalcaemia (according to total calcium <8.5).



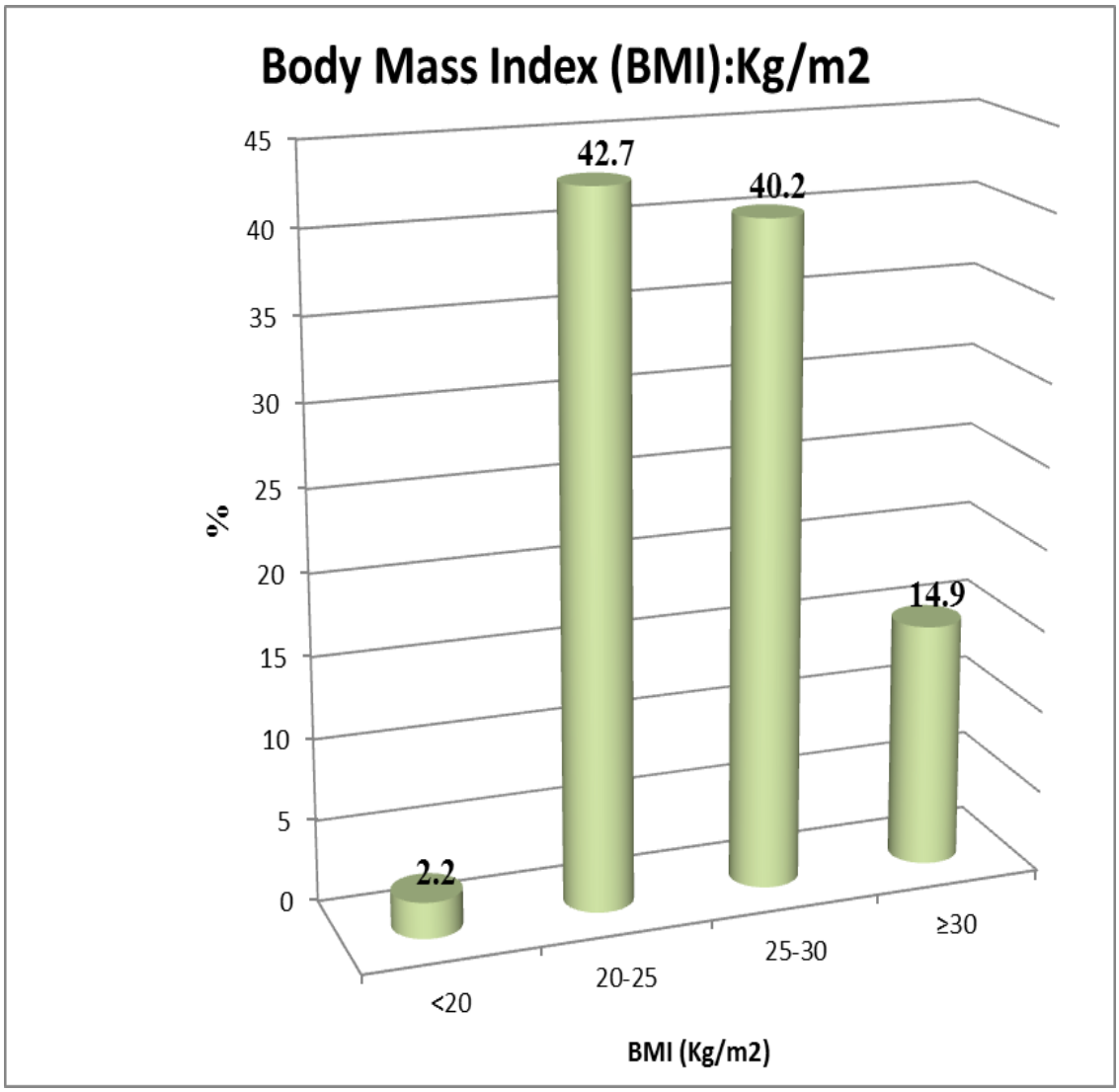
Nearly two-fifths of the women (42.7%) were normal weight, with a BMI ranging from 20 to <25 Kg/m2. Furthermore, 14.9% were obese, with a BMI of ≥ 30 Kg/m2 as shown in **table 2**. The relation between blood calcium and body mass index (BMI) is also shown in **table 2**. The table indicates the presence of a statistically significant differences between these two variables, p=0.007. It can be noticed that higher values of BMI were associated with higher levels of blood calcium.

Table (2): Distribution of study women according to Body Mass Index and relation between Maternal serum calcium of pregnant women & their BMI .

	Frequency	**Percent**	**Blood Ca(mg/dl) Mean ±SD**	**P-value**
Body Mass Index (BMI): Kg/m^2				
Underweight, <20	11	2.2	6.8±0.9	
Normal, 20-25	214	42.7	8.8±1.8	**0.007***
Overweight, 25-30	200	40.2	8.9±1.5	
Obese ≥30	75	14.9	9.3±1.6	

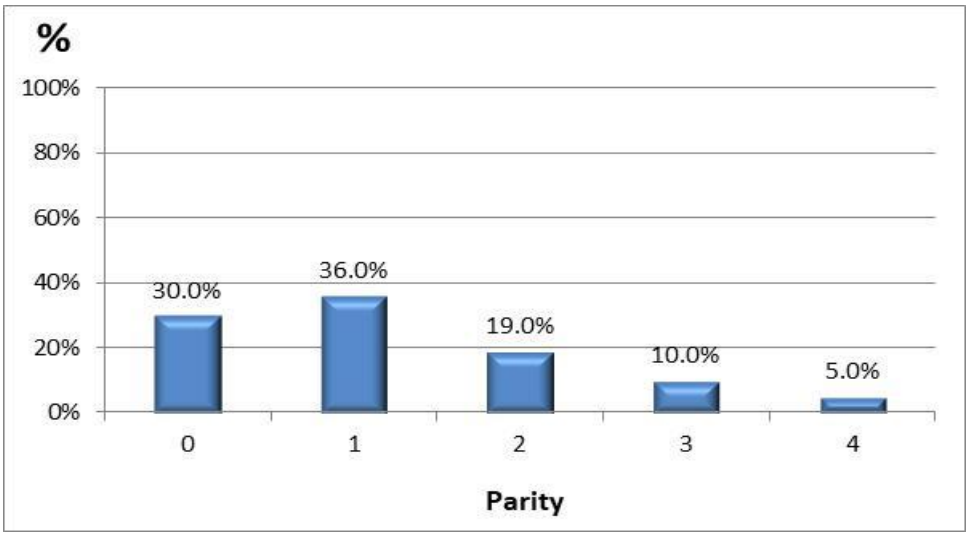
Distribution of our study women according to their Body Mass Index is shown in **figure 3**

Figure (3): Distribution of study women according to Body Mass Index



Concerning obstetric history, about two-thirds of the study women had parity less than 2 i.e., 330 (66.0%), while (5%) were grand-multiparas as in **Figure 4**.

Figure (4): Distribution of study women according to number of Parity.



In our study results we found that the prevalence of hypocalcaemia was high in parity less than 2, with statistically significant p-value (0.034) as shown in **table 3**.

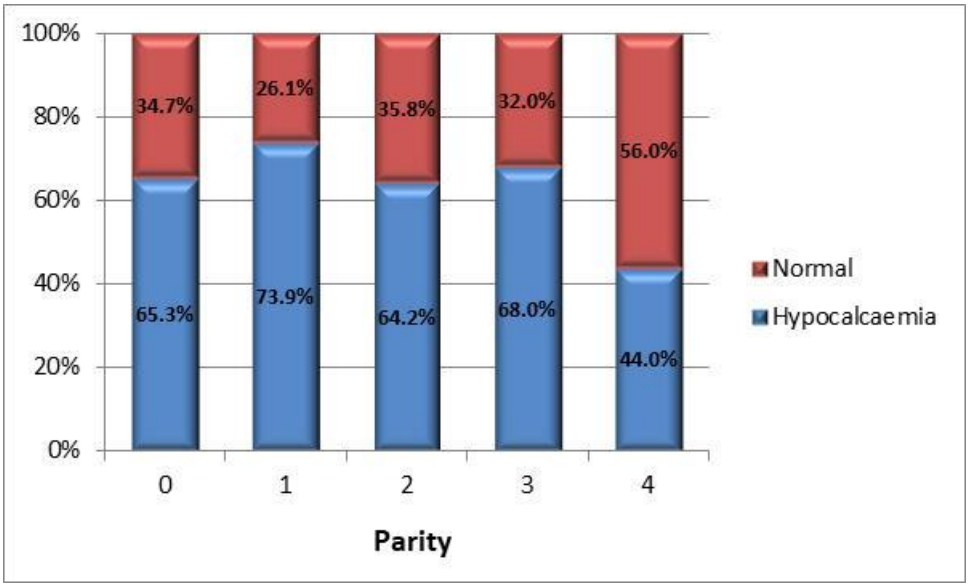
Table (3): Relation between Parity and hypocalcaemia

Parity	**Normal**		**Hypocalcaemia**		**P-value**
	N	**%**	**N**	**%**	
0	52	34.7%	98	65.3%	
1	47	26.1%	133	73.9%	
2	34	35.8%	61	64.2%	**0.034**
3	16	32.0%	34	68.0%	*****
4	14	56.0%	11	44.0%	

***Significant**

The prevalence of hypocalcaemia was high in all study women regardless to their parity with higher incidence in low parity than in grand multipara as in **Figure (5).**

Figure (5): Relation between Parity and hypocalcaemia



There was correlation between ionized calcium and maternal age with statistically significant p-value 0.001. There was also correlation between total calcium and gestational age with statistically significant p-value 0.037. In contrast the correlation between total and ionized calcium and Hb% is of no statistical significance as in **table 4.**

Table (4): Correlations between total and Ionized calcium with age, gestational age and Hb%.

	Total Ca+		**Ionized Ca+**	
	r	**P-value**	**r**	**P-value**
Age (years)	0.035	0.431	**0.151**	**0.001***
Gestational age (weeks)	**-0.103**	**0.037***	-0.084	0.060
Hb%	0.012	0.794	-0.053	0.233

***Significant**

4. Discussion:

Calcium homeostasis is a complex process regulated by, two calcitropic hormones, PTH and calcitonin along with 1, 25 (OH)2 D3. The significant decrease of serum Ca^{+2} occurs in mid pregnancy when there is an elevated fetal requirement in the presence of inadequate intestinal absorption and/or insufficient

maternal intake [10]. Calcium deficiency has several impacts in females from the fetal phase to the elderly post-menopausal age as the body has increased Ca^{+2}demands during growth spurts,

pregnancy as well as lactation. InsufficientCa^{+2}intake may, therefore, lead to many problems particularly in growing children and adolescents; this may result in stunted growth, and a decreased peak bone density thus elevates the risk of osteoporosis later.

Females are at risk if they already have decreased serum Ca^{+2}level and must undergo the strain on their bodies to meet the normal maternal requirements with additional demands of Ca^{+2} during pregnancy and lactation.

In our study we found that nearly2/3 of pregnant females were hypocalcaemic (67.4%). None of the females with hypocalcaemia had any overt symptoms of hypocalcaemia.

No determinants (education, age, dietary intake of Ca^{+2}, weight, height, BMI, and Hb levels) found in our study which might be explained by the high incidence of hypocalcaemia.

We found in our study that the prevalence of hypocalcaemia was more in young aged females and of low parity of almost normal body weight.

A study [5] in **India**, reported the prevalence of hypocalcaemia in pregnant females was 66.4% (n = 362/545); all being asymptomatic. The daily dietary Ca^{+2} intake being less than the recommended dietary allowances was a most probable cause of the hypocalcaemia

A similar study was conducted in the Littoral Region of **Cameroon** by [10] a hospital-based cross-sectional study targeting women in late pregnancy. The prevalence of hypocalcaemia in late pregnancy was 59%

The **Institute of Medicine (IOM) committee** concluded that any calcium deficit not provided by an increased efficiency in calcium absorption could be supplied by mobilizing maternal bone calcium, based on data from one cross-sectional study of postpartum women. It was assumed that maternal bone loss to support the demands of both pregnancy and lactation are recovered by 1 year postpartum. The most recent IOM report (November 2010) upheld the previous recommendation for dietary calcium intake during pregnancy [11]. A prospective study was conducted in **Algeria** by [12], about calcium deficiency among pregnant women and their newborns showed that the prevalence of hypocalcaemia in pregnant women was 70.55%. Their patients were aged 17 to 50 years. Their statistical results showed that most of them (73%) were aged between 21 and 35 years.

Also there search showed that approximately 53.71% of low birth weight infants developed early hypocalcaemia, and 79.09% of preterm suffered from hypocalcaemia. That was

higher to the research conducted in the United States, because the prevalence of hypocalcaemia in full-term infants was 30 to 40 percent. Also, it was still higher than that found in Iran where reported rate is 22.4% [12]. Our study limitation was on the impact of hypocalcaemia on pregnancy outcome as preeclampsia, eclampsia, preterm labor and IUGR. That was noticed by many studies showing high association between hypocalcaemia and adverse pregnancy outcomes.

New studies were done about relation of hypocalcaemia and preeclampsia as in **Bangladesh** a study by [13] showed significantly lower levels of calcium in pre-eclamptic women. They gave an opinion that early detection and supplementation to treat this deficiency may reduce the incidence of preeclampsia.

Another recent study in **Pakistan** done by [14] had indicated that low levels of serum calcium in women presenting with preeclampsia and frequency of hypocalcaemia was very high. The prevalence of hypocalcaemia was 60% in patients with preeclampsia. Low serum calcium level was associated with increasing age, poor socioeconomic status, increasing parity, family history of preeclampsia and previous history of preeclampsia. All the preeclamptic women should be screened for serum calcium levels and be managed accordingly to avoid future feto maternal adverse outcomes **.**

Also a study by [15] showed intake of supplements, mainly calcium may help in the reduction of incidence of pre-eclampsia especially in a population of a developing country where the nutrition is poor .

Another meta-analysis was done on effect of hypocalcaemia on pregnancy of ten trials (2234 females) reported that supplementation with low doses of Ca^{+2}significantly reduce the risk of preeclampsia. Also there was a reduction in hypertension, low birth weight, and neonatal intensive care unit admission [16]**.**

Another study by [17] reported that maternal Ca^{+2} metabolic stress along with low Ca^{+2}intake or inadequate vitamin D, has an adverse effect on fetal growth **.**

Although other studies show no significance of hypocalcaemia on pregnancy as, [18] observed that there was no significant difference in the serum levels of calcium, magnesium and zinc levels in the 40 normotensive pregnancies (controls), 20 mild and 20 severe preeclamptic Iranian women**.**

Also a cross-sectional study subjects of eighty pregnant women living in Abakaliki, **Nigeria,** showed no significant decrease of serum calcium levels in pre-

eclamptic women compared to normal pregnancy [19]**.**

5. Conclusion and Recommendations:

This study shows that 2/3 of pregnant females had asymptomatic hypocalcaemia that was unrelated to nutritional and socio-economic status as well as daily Ca^{+2} intake.

So, routine maintaining of serum calcium levels during pregnancy should be used as a preventive method that may help in reduction of incidence of hypocalcaemia especially in a developing country like ours where nutrition is poor.

Further research is needed to determine the path physiological mechanisms of such elevated incidence of hypocalcaemia and its influence on the long-term health of the mother as well as child.

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