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EFFECT OF IRON DEFICIENCY ANEMIA (IDA) ON THYROID FUNCTION AND HAEMATOLOGICAL PROFILE IN PREGNANCY

Biochemistry

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ABSTRACT

Background: Anemia and thyroid disorders, both are common public health problems with pregnant women being the most vulnerable group. The risk of maternal mortality has a direct correlation with the severity of IDA (Iron Deficiency Anemia). Some previous studies suggested that iron deficiency anemia is related to thyroid function in pregnancy. **Objectives:** To evaluate the prevalence of anemia and evaluate the level of thyroid hormones in pregnant women and to study inter-relationship of iron deficiency anemia with other hematological parameters and thyroid hormones in pregnancy. **Materials and methods:** A total of 100 antenatal cases of women were included, with the reproductive age group of 20-40 years. Subjects were categorized into three trimesters of pregnancy, viz. first trimester, second trimester and third trimester and their blood samples were analysed for biochemical and hematological parameters. **Results:** In the present study, it has been observed that 57% of pregnant women were anemic with Hb <11 g/dl. Based on the haematological studies, the anemic condition was due to the deficiency of iron. Further, thyroid function was found to be correlated with iron deficiency anemia. Subclinical hypothyroidism was found in 49% of anemic subjects. **Conclusion:** From the results of present study, it is concluded that there is increased prevalence of thyroid disorders and iron deficiency anemia in antenatal cases and there is relationship between iron deficiency anemia and hypothyroid cases. Subclinical hypothyroidism is more pronounced effect than overt hypothyroidism due to iron deficiency anemia in pregnancy as revealed from the data generated in the study. Screening of thyroid stimulating hormone in all pregnant women at time of first visit and treatment should be started if TSH <2.5IU/ml for healthy feto-maternal outcome. It has been established from the present study, that anemia can worsen this condition further, since iron deficiency being a from the present study, that anemia can a major public health problem in developing country like India.

KEYWORDS

Iron Deficiency Anemia, Pregnancy, TSH, T4, T3, Body Mass Index.

INTRODUCTION

Pregnant women are often iron deficient, and iron deficiency (ID) has adverse effects on thyroid metabolism. Impaired maternal thyroid function during pregnancy may cause neurodevelopmental delays in the offspring. ID has multiple adverse effects on thyroid metabolism. It decreases circulating thyroid hormone concentrations, likely through impairment of the heme-dependent thyroid peroxidase (TPO) enzyme. Anemia in pregnancy is a decrease in the total red blood cells (RBCs) or haemoglobin in the blood during pregnancy or in the period following pregnancy. It involves a reduction in the oxygen carrying capacity of the blood. Anemia is an extremely common condition in pregnancy and postpartum world-wide, conferring a number of health risks to mother and child (Pavord et al, 2012).

Anemia can be congenital (i.e., conditions such as sickle cell anemia and thalassemia) or acquired (i.e., conditions such as iron deficiency anemia or anemia as a result of an infection) (NHLBI 2018). Anemia is the most common deficiency disease in the world, affecting 1.62 billion people globally corresponding to 24.68 % of the world population (Toteja et al, 2006). According to the WHO (World Health Organization), anemia is taken as a disease of low public health importance when the prevalence is less than 20%, of medium public health importance, when it is between 20 to 39.9% and severe when the prevalence is 40% and more in the population (Toteja et al, 2006). Present study was conducted with the aim to assess the prevalence of anemia in women during pregnancy and to investigate their thyroid levels and haematological profile.

MATERIALS & METHODS

A total of 100 women with ideal maternal age who attended regular prenatal healthcare at Arora Hospital, Amritsar and Sachdeva Nursing Home, Amritsar were included in this study. Details of patients particulars, personal, family, menstrual and obstetric history of the patients in the proforma was obtained along with general and obstetrical examination findings. After proper counselling all the cases were underwent routine antenatal investigations along with the thyroid profile including serum TSH, T3, T4. Along with these serum levels of iron, TIBC, UIBC and Transferrin Saturation (%) and CBC Parameters including Hb, HCT, RBC, MCV, MCH, MCHC, Platelet count were done. The blood samples were proceeded in the department of Medical Laboratory Sciences, Khalsa College of Pharmacy and Technology, Amritsar (Punjab). Group wise distribution of subjects were done as: Group-1: Normal Control Group-2: Anemia Group-3: Severe Anemia. The women were categorized into 3 groups depending upon the haemoglobin level as recommended by WHO (World Health Organisation) as Normal >11 g/dl, Anemic 8.1-10.9 g/dl, Severe anemia < 8g/dl.

Blood was collected by veinpuncture method (Godkar, 2007) Samples were centrifuged at 3000 rpm, separated and preserved at 4°C for further analysis. For hematological analysis, the kits were from the Coral Clinical Systems and the tests were performed manually using a semi auto analyzer. CBC was performed manually using a Mindray autoanalyzer. The sample was agitated to evenly distribute the cells, then diluted and partitioned into at least two channels, one of which was used to count red blood cells and platelets, the other to count white blood cells and determined the hemoglobin concentration. The cells were suspended in a fluid stream and their properties were measured as they flow past sensors in a technique known as flow cytometry. Iron was determined by Ferrozine method (Siedel et al, 1984) The serum iron was estimated on semi biochemistry auto-analyzer by using a commercially available kit (Coral Clinical Systems). Iron, bound to Transferrin, was released in an acidic medium and the ferric ions were reduced to ferrous ions. The Fe (II) ions reacted with Ferrozine to form a violet-colored complex. Intensity of the complex formed was directly proportional to the amount of iron present in the sample. Total iron binding capacity (TIBC) was determined by Ferrozine method (Siedel et al, 1984). For TIBC, the serum was treated with excess of Fe (II) to saturate the iron binding sites on transferrin.

The excess Fe (II) was absorbed and precipitated and the iron content in the supernatant is measured to give the TIBC. Unsaturated Binding Iron Capacity (UBIC) was calculated from TIBC and iron by using following formula: Calculations: UBIC in µg/dl = TIBC in µg/dl -Iron in µg/dl. Normal references values: UBIC (Females): 160-360 µg/dl 3.4.5. Iron (transferrin) Saturation% Iron (transferrin) Saturation was calculated from Serum Iron and TIBC by using following formula: Calculations: Iron (transferrin) Saturation = Normal references values: Iron (transferrin) Saturation (Females): 15-50%.The level of thyroid stimulating hormone (TSH) in serum was determined by CLIA method. The kits for the thyroid analysis were from the Snibe Diagnostic and the tests were performed manually using a MAGLUMI series Fully-auto chemiluminescene immunoassay analyzer (MAGLUMI Snibe-600).

RESULTS & DISCUSSION

In present study, we have used trimester specific reference ranges for thyroid tests, reference ranges for iron deficiency anemia,

haemoglobin cut off for anaemia as per ICMR, and reference ranges for various indicators of iron deficiency anemia. The reports of the cases were assembled and compared to see the relationship between thyroid disorder and iron deficiency anemia in pregnancy. The mean age and basal metabolic index (BMI) of the subjects enrolled in the study were comparable to each other (Figure No. 1). in all three trimesters of pregnancy. It can be seen from the data, pregnant women with severe anemia had lower than normal BMI, specifically in first and second trimester of pregnancy. Our results showed that, in first trimester, the mean Hb of normal group is 11.69±0.63 g/l, whereas in anemic group, it was found to be 10.03±0.52 g/l. However, in third group of severely anemic category, the mean Hb level was 7.16±0.54 g/l, in first trimester. It has been observed that, 57% of pregnant women were found to be anemic in studied population. This percentage ranges from 35-75% in specific areas, and is much higher than the 18% of pregnant women diagnosed with anemia in developed countries. Iron deficiency during pregnancy is thought to be caused by combination of factors such as previously decreased iron supply, the iron requirements of the growing fetus, and expansion of maternal plasma volume (Laflamme 2011). It has been observed that, 69% of pregnant women was found to be anemic (Hb<11g/dl) in the second trimester of pregnancy among the enrolled subjects in the present study. Furthermore, it has been seen that 7% of pregnant women were having Hb> 8g/dl. It has been observed that, 36% of pregnant women was found to be anemic (Hb<11g/dl) in third trimester of pregnancy. Low levels of haemoglobin (anemia) early in pregnancy or during pregnancy, caused either by previous anemia or the anemia occurred during pregnancy can predispose the mother to infections, hypoxia or oxidative stress and thereby lead to preterm delivery. The proposed explanation for this relationship was the lower socioeconomic and nutritional condition in these mothers. The findings suggested that, particularly in the first and second trimesters, pregnant women with severe anemia had BMIs that were lower than average. During first and second trimesters, the BMI of pregnant women with severe anemia was lower than the average (Fig. 1).

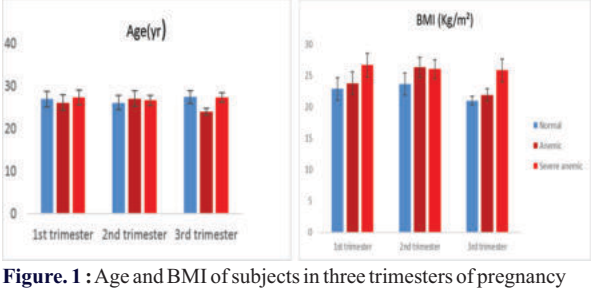

Figure. 1 : Age and BMI of subjects in three trimesters of pregnancy

Pregnancy causes the plasma volume to expand more than the red cell mass, which results in a decrease in haemoglobin concentration, hematocrit, and red blood cell count. However, the increase in red cell mass is directly correlated with an increase in the total amount of circulating haemoglobin. The individual's iron status also plays a role in this. It is advised that pregnant women have a sufficient amount of haemoglobin for this reason.

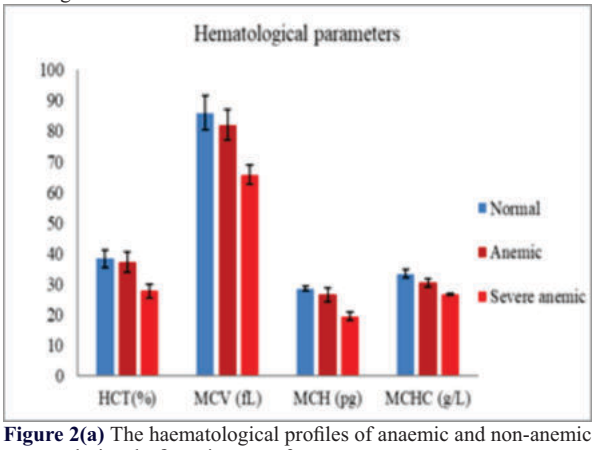

Figure 2(a) The haematological profiles of anaemic and non-anemic women during the first trimester of pregnancy.

Table 1 : Haemoglobin and RBC content in different studied groups in three trimesters of pregnancy.

Group	Population (η)	Hb (g/L)	RBC (*10^{12}/L)
First Trimester			
Normal	14	11.69±0.63	4.35±0.23
Anemic	12	10.03±0.52	3.82±0.07
Severely Anemic	7	7.16±0.54	3.41±0.08
Second Trimester			
Normal	13	11.07±0.67	4.29±0.27
Anemic	26	10.06±0.52	3.82±0.06
Severely Anemic	3	7.07±0.51	3.44±0.04
Third Trimester			
Normal	9	11.83±0.76	4.46±0.29
Anemic	13	10±0.41	3.8±0.08
Severely Anemic	3	7.13±0.25	3.16±0.18

*Data represented as Mean ±S.D.

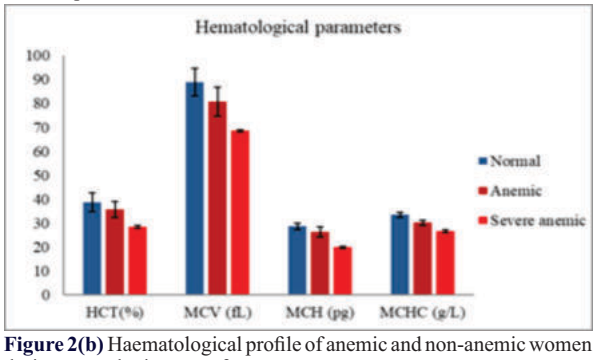

Figure 2(b) Haematological profile of anemic and non-anemic women during second trimester of pregnancy.

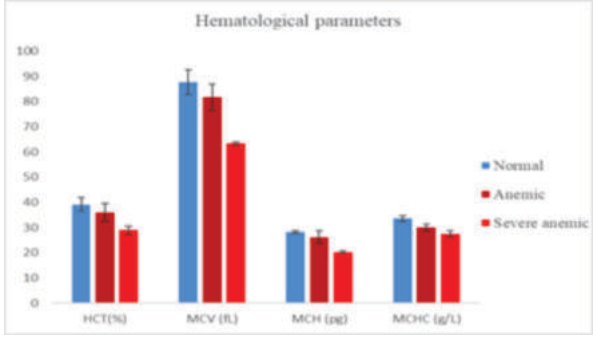

Figure 2(c) Haematological profile of anemic and non-anemic women during third trimester of pregnancy.

Figure 2 illustrates the various CBC parameters, including as the HCT, MCV, MCH, and MCHC levels, among the various study groups throughout the first trimester of pregnancy. Our findings demonstrated that, Hb lesser than 8 g/dl severly affected haematological profile of pregnant women in all three trimesters whereas anemic patients having Hb 8 to 10 g/dl did not showed much differences when compared to control.

Table 2: Serum iron levels, total iron binding capacity (TIBC), unsaturated binding iron capacity (UBIC), and saturation (TS%) in three trimesters of pregnancy

Group	S.Iron µg/Dl	TIBC µg/dL	UBIC µg/dL	Saturation (TS%)
First Trimester				
Normal	36.68±1.95	192.41±14.81	155.73±9.92	19.35±1.13
Anemic	32.16±1.67	197.37±16.63	168.16±13.31	16.13±1.17
Severely anemic	19.78±0.35	139.54±7.39	118.47±4.49	12.53±0.36
Second Trimester				
Normal	44.53±1.86	196.04±15.67	151.51±8.77	23.02±2.13
Anemic	32.05±1.74	182.35±9.56	150.30±7.78	18.71±1.38
Severely anemic	19.49±0.21	156.9±7.40	137.41±4.48	12.37±0.20
Third Trimester				
Normal	38.31±2.31	187.88±12.03	149.57±6.28	20.92±1.01
Anemic	28.44±1.55	161.60±9.38	133.16±5.14	17.77±0.95
Severely anemic	14.39±0.21	138.72±3.71	124.33±3.96	10.33±0.76

***Data represented as mean ±S.D.**

Serum levels are differentiated based on Hb ranges. iron as well as every other parameter. During the first trimester, S.Iron and Transferrin saturation (%) were within normal limits in the control group. The TIBC and UBIC levels in the normal group were noticeably low. Furthermore, in pregnant anaemic women. Despite low iron and TIBC levels, UBIC and Transferrin Saturation (%) levels were low. S.Iron, TIBC, UBIC, and Transferrin Saturation (%) were also reduced in extremely anemic pregnant women.The second trimester is when the S. Transferrin saturation (23.02±8.13%) and iron (44.53±18.86) levels were normal, but TIBC (196.04±45.67) and UBIC (151.51±41.77) levels were low. S.iron, TIBC, UBIC, and Transferrin Saturation (%) levels were significantly lower in second-trimester extremely anaemic pregnant women.

Table 3: Thyroid profile of anemic patients in three trimesters of pregnancy

	TSH µIU/L	T3nmol/L	T4 nmol/L
First Trimester			
Normal	2.24±0.19	1.78±0.15	77.97±2.49
Anemic	2.37±0.27	1.78±0.18	81.97±2.57
Severely Anemic	2.00±0.16	2.11±0.22	73.68±1.94
Second Trimester			
Normal	2.89±0.23	2.37±0.11	91.36±2.12
Anemic	3.21±0.69	2.37±0.16	86.53±1.18
Severely Anemic	2.15±0.76	2.30±0.12	87.33±1.36
Third Trimester			
Normal	2.94±0.57	2.19±0.11	90.76±2.77
Anemic	2.86±0.49	2.23±0.12	91.89±3.40
Severely Anemic	3.19±0.62	2.56±0.14	82.77±1.80

***Data represented as mean ±S.D.**

In this study, by tracking the TSH mean value for each trimester, we noticed that the TSH value in the first trimester is lower than in the second trimester while the third trimester has the highest value during pregnancy. The initial decrease in TSH value is likely due to human chorionic gonadotrophine with its TSH mimetic effect that is characteristic in early pregnancy. With fading up of human chorionic gonadotrophine effect with advancing pregnancy, the TSH concentration starts to rise to reach its highest concentration in late pregnancy. This upward sloping curve in the TSH level was also observed in anemic cases, as they were found to be increased in subjects with anemic pregnancy in both second and third trimesters.

The increased TSH levels and decreased fT3 and fT4 levels indicates hypothyroidism. Earlier studies also reported that hypothyroidism is the most common pregnancy-related thyroid disorder, affecting 3-5% of all pregnant women. Growing researches suggests that iron deficiency with or without anemia impairs thyroid metabolism by decreasing plasma T3 and T4, reducing peripheral conversation of T4 to T3 and increasing TSH concentration (Shuxiang *et al,* 2016).

In the first trimester, 33 antenatal cases were enrolled and the T4 level was normal in normal group 77.97±21.49 nmol/L, anemic group 81.97±32.57 nmol/L and severely anemic group 73.68±29.19 nmol/L of pregnant women. On the other hand, 42 pregnant women were involved in the second trimester, and the level of T4 was 91.36±14.12 nmol/L in normal pregnancy, whereas the values got diminished in case of pregnant women with anemia. The mean level of T4 was 86.53±38.88 nmol/L and 87.33±15.36 nmol/L in anemic and severely anemic pregnancies, respectively. On the other hand, in the third trimester, 25 pregnant women were enrolled, it was observed that T4 level was 90.76±20.77 nmol/L and 91.89±43.40 nmol/L in normal and anemic group, however, T4 level in the case of severely anemic pregnant women was significantly low 82.77±27.80 nmol/L.

Tetra-iodothyronine (T4) and tri-iodothyronine (T3) both increased during pregnancy in the second and third trimester. All three of these thyroid function differences between trimesters are statistically different. The values of both total T3 and total T4 increase from the first trimester to the second trimester, and then this increase nearly plateaus, with minimal reduction at the end of pregnancy. This could be due to the increased binding effect of TBG, which tends to increase with advancing pregnancy.

Table 4 depicts the prevalence of thyroid dysfunction among three groups of pregnant subjects. It has been observed that in early pregnancy, 16% pregnant women with anemic condition were found with overt hyperthyroidism. In second and third trimester, negligible (0.03% in first trimester and 0.06% in second trimester) cases of overt hyperthyroidism were found. However, it can be seen from the data, no any case of overt hyperthyroidism was found in pregnant women with normal hematological indices.

Based on diagnostic criteria, overt hypothyroidism which is defined as elevated TSH concentration with diminished serum T4 concentration, it has been estimated that upto 31% of pregnant women in first trimester, 34% of pregnant women in second trimester and 37% of pregnant women in third trimester, with anemic conditions, were affected with overt hypothyroidism. As Overt hypothyroidism has a definite adverse effect on obstetric and child development outcomes during pregnancy, the 2017 ATA guidelines recommend that it should be treated as early as possible.

Subclinical hypothyroidism is more common than is overt hypothyroidism, and is usually defined as a serum TSH concentration greater than the pregnancy-specific reference range for each laboratory value, or by serum TSH concentrations greater than 2·5 mIU/L in the first trimester and greater than 3 mIU/L in the second and third trimesters, respectively. It has been observed that, in early pregnancy TSH levels were less than 2.5 mIU/L in normal and anemic cases. However, it has been revealed from the individual data, in second and third trimester, maximum anemic cases with low Hb and iron deficiency depicted TSH levels greater than 3 mIU/L, which indicated subclinical hypothyroidism. Subclinical hypothyroidism, defined as elevated TSH and normal T4 concentration in serum, was found in 5 cases of anemic pregnancy (21%) during first trimester. Also, 5 cases of subclinical hypothyroidism (17%) were found in second trimester, and 4 cases were found in third trimester. On the contrary, it has been observed that only one case of subclinical hypothyroidism was seen in normal pregnancy during first and second trimester, and no any case has been observed in third trimester. It has been observed that subclinical hyperthyroidism was found in three cases of anemic pregnancy in second trimester, whereas only one case has been observed during first and third trimester in pregnancy.

Iron deficiency anemia affected thyroid hormone status leading to thyroid dysfunction by decreasing plasma T3 and T4, reducing peripheral conversion of T4 to T3, and increasing TSH concentrations. Iron deficiency may affect thyroid metabolism by inducing alterations in common hypothalamic pituitary thyroid axis, reducing T3 binding to hepatic nuclear receptors (Smith *et al,* 1993), or through anemia and lowered oxygen transport (Surks 1969). Iron deficiency may also impair the activity of hepatic T4-5' deiodinase, an enzyme responsible for the conversion of T4 to T3 (Brigham and Beard 1995), or the activity of thyroid peroxidase, which is iron dependent and responsible for thyroid hormone synthesis (Hess *et al,* 2002). A recent controlled trial study in iron deficient adolescent girls indicated that improvement of iron status was accompanied by an improvement in some indices of thyroid hormones including T4, T3 (Eftekhari *et al,* 2006). However, the mechanism between anemia and thyroid function remains unclear; a few studies have shown that the mechanism by which ID affects thyroid function is likely to impair the efficacy of iodized salt and TPO activity as well as the conversion of T4 to T3.

Applying regression analysis between TSH and Hb level, there was a positive correlation between these two factors in cases. r2 value was found to be 0.2718. This was statistically significant with a P value of less than 0.005.

These findings are compared with a study done by (Dhanwal *et al,* 2016). They reported prevalence of hypothyroidism in pregnancy was 13.13% and major being subclinical. In a study by Agarwal *et al* 2016, the prevalence was 31.8%. (Chowdhary *et al*, 2021) reported 21% prevalence of hypothyroidism in their study. Our findings are more or less correlated with the above studies.

Table :4 Thyroid dysfunction and iron deficiency anemia in pregnant women in all trimesters of pregnancy

Iron Deficiency Anemia	Thyroid dysfunction			
	Overt Hyperthyroidism	Overt Hypothyroidism	Subclinical Hyperthyroidism	Subclinical Hypothyroidism
	TSH↓ T4↑	TSH↑ T4↓	TSH↓ T4 n	TSH↑ T4 n

First trimester				
Normal	0	3	0	1
Anemic	2	4	1	3
Severely Anemic	1	2	1	1
Second trimester				
Normal	0	3	1	1
Anemic	1	9	3	4
Severely Anemic	0	1	0	1
Third trimester				
Normal	0	3	0	0
Anemic	1	5	0	3
Severely Anemic	0	1	1	1

CONCLUSION

According to the study's findings, prenatal cases of thyroid problems and iron deficiency anaemia are more common, and there is a link between these conditions and cases of hypothyroidism. The study's data showed that subclinical hypothyroidism is a more severe consequence of iron deficient anaemia in pregnancy than overt hypothyroidism. All pregnant women should be screened for thyroid stimulating hormone at the time of their first appointment, and therapy should begin if the TSH level is below 2.5 IU/ml for a healthy feto-maternal outcome. Since iron deficiency is a serious public health issue in developing nations like India, it has been demonstrated from the current study that anaemia can deteriorate this condition even worse.

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