Subclinical Hypothyroidism and Accidental Hemorrhage

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Abstract

Back ground: *Subclinical hypothyroidism* (SH) is defined by an elevated serum thyrotropin level and *normal* serum thyroxine concentration. While strong evidence clearly demonstrates that overt dysfunctions (hyper- or hypothyroidism) have deleterious effects on pregnancy outcome, subclinical disease, namely subclinical hypothyroidism, has still to be conclusively defined as a risk factor for adverse outcomes˙, of those bad obstetric outcomes, placental abruption (PA) (accidental hemorrhage) is associated with underlying risk factors both jeopardizing trophoblast and vascular function. Subclinical hypothyroidism may relate to both conditions. Aim of study: to prove the association between subclinical hypothyroidism and placental abruption(accidental hemorrhage) in study group compared to control group.

Setting: a prospective case controlled study involves total 109 laboring women, who attended Al-Zahra teaching hospital at Annajaf city-Iraq between March to September 2013.

Patients and methods:of total 109 women entered our study, 54 with normal labour and were regarded as control group and 55 with clinical diagnosis of placental abruption, after complete history and examination, blood sample withdrawn and thyroid function test, TSH, T3, T4, and free T4 were measured using commercially available Minividas kits (*biomerieux*, France), Minividas was performed according to manufacturer instructions. The normal value for T3 was (0.95-2.23), T4 (60-120) and TSH (0.25-5) µIU/ml and freeT4 (0.76-2.24). Those who had high TSH and low T3, T4 and free T4 when compared to laboratory specific normal values, were diagnosed as clinical (overt) hypothyroidism, and were excluded from our study. those who had high TSH but normal freeT4 thyroid hormone were diagnosed to have subclinical hypothyroidism, those in whom all hormone values were within normal limits were designated as euthyroid. **Statistical analysis:** These were used to accept or reject the statistical hypotheses, they include the followings: ANOVA test (F-test) and (chi square test). The comparison of significant (P-value) in any test were S= Significant difference (P≤ 0.05). Results:

Of total 109 participants 54 regarded as control while 55 were diagnosed clinically as cases of PA, there were no statistical significant difference between two groups in maternal age with mean maternal age of 27.92±5.42 SD and 27.49±6.58 SD for control and PA respectively,   low parity dominated the picture for both groups and although the ratio of those who were P0-P2 was higher in cases of PA 92.7% compared to control group 87.7%this did not reach statistical significance with P value of 0.09, most of our participants were urban and there were no statistical clinical significance between two groups with figures of 76.3% and 79.6% for PA and control groups respectively, but there was statistically significance difference in gestational age between our study groups with PA tends to occur at smaller gestational age 34.67 weeks±3.39 SD compared to control group 37.57 weeks±1.57 SD, surprisingly there was nearly fourfold rise in incidence of SH in patients with PA compared to control group with ratio of 16.3% and 3.7% for PA and control group respectively. And again there was no statistical significance in identification of SH for those who were term or preterm in PA group (17.6% vs 15.1%).

Discussion: subclinical hypothyroidism was identified in 3.7% of the control population tested, and this corresponds with all previous reports 2% to 5% in pregnant women. however, this ratio increased to 16.3%, 9/55 (nearly fourfold) of cases diagnosed with clinical abruption a figure which was higher than reviewed in previous reports of 2-3 fold rise incidence of placental abruption with subclinical hypothyroidism. This results agree with Casey and colleagues who studied pregnancy complications with SH, who found that Significantly more placental abruptions (relative risk [RR], 3.0; 95% CI, 1.1-8.2), were found in the SH group, but disagree with Cleary-Goldman and colleagues who reported on First and Second Trimester Evaluation of Risk (FASTER) trial, in which the researchers found no increased risk of placental abruption. Unlike Brian M. Casey, who found that women with subclinical hypothyroidism were significantly older than control women[3], in this study there was no statistically significant difference in mean maternal age between two groups, there were also no significant differences in other demographic variables like residency and parity,however; gestational age (GA) was significantly lower for cases PA, but when gestational age studied in relation to placental abruption with SH at term and preterm gestational ages 3/17 vs 6/38 respectively, this failed to reach statistical significance.

Conclusion:

1-SH is not uncommon condition among our laboring population

2-SH was found to increase fourfold risk of placental abruption in this study

3-maternal age, parity, residence all were insignificant confounders between control and PA group

4- placental abruption tends to occur at preterm gestational age but this failed to reach statistical significance for

cases with SH in term and preterm GA.

Introduction

subclinical hypothyroidism and placental abruption

in spite of the overwhelming efforts offered by Iraqi ministry of health in facing health challenges and the remarkable improvement in health services overall , our country is still lacking an organized and effective screening for number of diseases that can adversely affect maternal and perinatal outcome, and indeed still a lot of pregnancies are lost at various stages of pregnancy, labour, early and late neonatal period without knowing the exact cause for such bad outcomes. And one of these important health issues that requires strict guidelines adherence is thyroid dysfunction.

Thyroid disorders are among the most common endocrinopathies encountered during pregnancy. Hyperthyroidism accounting for approximately 0.5% to 1% and hypothyroidism for 2.5% to 3%[1] . Hypothyroidism is even more common in the setting of iodine deficiency approaching in one study as high prevalence as 6.3% in developing country, India[2]. Clinical thyroid dysfunction has been associated with pregnancy complications such as hypertension, preterm birth, low birth weight, placental abruption, and fetal death. The relationship between subclinical hypothyroidism and pregnancy outcomes has not been well studied.[3,4]

The term subclinical denotes the presence of a disease without obvious symptoms, which means that evolution of the disease might be at an early stage. subclinical hypothyroidism is defined as an elevated serum thyroid stimulating hormone (TSH) level and a serum free thyroxine (FT_4) level that is within the normal laboratory and trimester-specific reference ranges. [1,5]In fact thyroid changes it's physiology during pregnancy and analysis of thyroid function tests (TFT) requires thorough understanding of these physiological changes prior interpretation.

The gland as whole increases in size and becomes more vascular, beta chorionic gonadotrophin (HCG) causes thyroid stimulation since 1st trimester due to structural analogy with thyroid stimulating hormone (TSH)[6]. The thyrotrophic activity of HCG causes also a decrease in TSH concentration so that pregnant women have lower serum TSH concentration than non pregnant women, the circulating level of thyroid binding globulin TBG are also increased by estrogen stimulation on the other hand the increased renal clearance, fetal intake and placental metabolism induce a relative decline in iodide bioavailability[7]. Total concentration of triiodothyronin (T3) and thyroxin(T4) increase in early pregnancy and achieve plateau early in 2nd trimester reaching a concentration value 30-100% greater than prepregnancy, primarily following the rise in TBG[8]. Some authors have reported a decrease in free T3 and T4 concentrations, whereas reported no change or even increase, therefore; changes in free hormones are controversial, though pregnant women have lower free hormones concentrations at term than non pregnant women. [9]
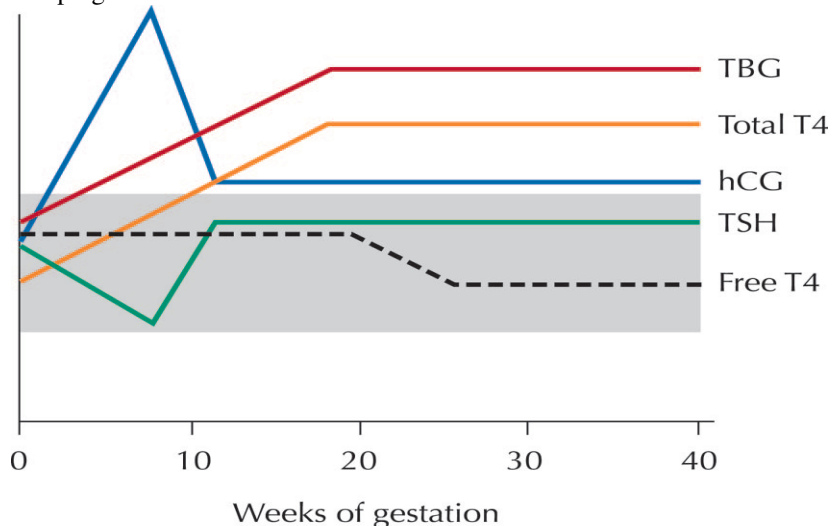

Fig. 1. The pattern of changes in serum concentrations of thyroid function studies and hCG according to gestational age. The shaded area represents the normal range of thyroid-binding globulin, total thyroxine, thyroid-stimulating hormone or free T4 in the nonpregnant woman.TBG, thyroid-binding globulin; T4, thyroxine; TSH, thyroid-stimulating hormone. Modified from Brent GA. Maternal thyroid function: interpretation of thyroid function[6]. Maternal thyroxine is particularly critical early in pregnancy because the fetal thyroid gland cannot synthesize iodothyronines until after 10 weeks of gestation. From this time onward, maternal as well as fetal thyroid hormones seem to be necessary for normal neurodevelopment.[10] It was reported that children of women whose TSH levels were elevated during the midtrimester of pregnancy had a slight but significant reduction in intelligence quotient (IQ) scores between 7 and 9 years of age when compared with infants of euthyroid women[10]. Women with TSH values more than 10 mU/L also had significantly more stillborn

infants. Somewhat related are previous reports that subclinical maternal hypothyroidism might be associated with poor pregnancy outcomes such as placental abruption, preterm birth, and low birth weight infants.[11,12]

The table below shows causes of subclinical hypothyroidism and differentiation from other causes of increases in serum TSH concentrations

Causes of persistent subclinical hypothyroidism
• Chronic autoimmune thyroiditis
• Partial thyroidectomy
• Radioactive iodine therapy for treatment of hyperthyroidism
• External radiotherapy of the head and neck in patients with Hodgkin's lymphoma,
leukaemia, aplastic anaemia, brain tumours, or bone-marrow transplantation
• Infi ltrative disorders of the thyroid gland (eg, amyloidosis, sarcoidosis,
haemochromatosis, or Riedel's thyroiditis)
• Persistent TSH increase after an episode of subacute thyroiditis, post-partum
thyroiditis, or painless thyroiditis
• Drugs impairing thyroid function in patients with autoimmune thyroiditis (iodine and
iodine-containing drugs, such as amiodarone and radiographic contrast agents,
lithium carbonate, cytokines [especially interferon alfa], or kinase inhibitors)
• Inadequate replacement therapy for overt hypothyroidism because of one of the
following reasons: inadequate dose; increased need for levothyroxine (increased body
weight and pregnancy); non-compliance; drug interactions (ferrous sulfate, calcium
carbonate, colestyramine, sucralphate, orlistat, possibly dietary soy and fibre, proton pump
inhibitors, aluminum hydroxide, ion exchange resins, raloxifene, or oestrogens);
increased T4 clearance (phenytoin, carbamazepine, or phenobarbital); malabsorption
(eg, *Helicobacter pylori* infection, coeliac disease, or atrophic gastritis); or toxic
substances, industrial, and environmental agents (eg, polychlorinated biphenyls)
• Thyroid dysgenesis
• Iodine defi ciency

Causes of physiological or transient increases in serum TSH concentrations
• Diurnal variation with a nocturnal surge and highest values early in the morning
• Recovery phase from non-thyroidal illness
• After withdrawal of thyroid hormone therapy in patients in euthyroid state
• Transient subclinical hypothyroidism after subacute, painless, or post-partum thyroiditis

**Causes of increased serum TSH concentrations that are not subclinical
hypothyroidism**
• Laboratory analytical problem (assay variability, abnormal TSH isoforms, or
heterophilic antibodies)
• Elderly patients with small increases in serum TSH concentrations
• Obesity
• TSH-secreting pituitary adenoma
• Isolated pituitary resistance to thyroid hormone
• TSH with reduced biological activity
• Impaired renal function
• Untreated adrenal insuffi ciency
• Serum TSH concentration outside of the reference range but normal for that
individual because the reference range only encompasses 95–97 · 5% of normal
individuals

TSH=thyroid-stimulating hormone. T4=thyroxine.

**Table. 1 causes of persistent SH, transient TSH elevation, and increased serum TSH concentrations that
are not subclinical hypothyroidism[13]**

Of the bad obstetric outcomes associated with SH to be elucidated in our study is placental abruption, and it is classically defined as complete or partial premature separation of a normally implanted placenta with hemorrhage into the decidua basalis[14], Symptoms of abruption vary immensely from an asymptomatic form in which the diagnosis is made only on placental inspection at delivery to massive abruption leading to fetal death and severe maternal morbidity, and it is the most common cause of pathological vaginal bleeding in late pregnancy.[15]The bleeding of placental abruption typically insinuates itself between the membranes and uterus, ultimately escaping through the cervix, causing external hemorrhage (65-80%). Less often, the blood does not escape externally but is retained between the detached placenta and the uterus, leading to concealed hemorrhage(20-35%)[16]. The diagnosis of placental abruption is always clinical [17,14], and the condition should be suspected in women who present with vaginal bleeding or abdominal pain or both, a history of trauma, and in

those who present with otherwise unexplained preterm birth or bloody amniotic fluid[14], although in most of the cases there is no identifiable underlying cause, many risk factors are blamed like   age, parity, race, familial factors, hypertension, prematurely ruptured membranes and preterm delivery, smoking, cocaine abuse, thrombophilias, trauma, leiomyomas, previously scarred uterus, anemia/folate deficiency and recurrent abruption.[18,15, 11]

it has been shown that individuals with subclinical hypothyroidism have impaired endothelium-derived vasodilatation from diminished nitric oxide secretion that is restored after thyroxine (T4) replacement[19], there is further evidence of vascular-related sequelae. Specifically, autoimmune thyroid disorders have been associated with an increased risk for placental abruption.[20]We designed this study to further elucidated the association between placental abruption and SH.

MATERIALS AND METHODS

prospective case controlled study involves total 109 laboring women, who attended Al-Zahra teaching hospital at Annajaf city between March to September 2013, 54 with normal labour and they were regarded as control group and 55 with clinical diagnosis of placental abruption (vaginal bleeding, uterine hypertonicity, blood stained liquor which were all later confirmed by presence of retroplacental clots after vaginal or caesarean birth) and were regarded as study group. After being consented to participate our study,   All patients underwent a comprehensive medical evaluation with complete history. Maternal age, parity, gestational age, residence, past obstetric history of adverse pregnancy outcome(i. e. early pregnancy loss, placental abruption, preeclampsia, intrauterine growth restriction, intrauterine death) past medical history of thyroid disease or type 1 diabetes, thyroidectomy, radioactive iodine therapy for treatment of hyperthyroidism, external radiotherapy of the head and neck , physical examination, including general examination, vital signs, BMI, examination for clinical goiter, maternal and fetal condition assessed as well labour stage, blood sample withdrawn as for routine management of labour, placental abruption and thyroid function test, TSH, T3, T4 and free T4, cases with overt thyroid dysfunction overt hyper/or hypo-thyroidism diagnosed by history and abnormal thyroid function test were excluded from our study.It was made sure that being involved in this study did not delay the urgent management of accidental hemorrhage, as withdrawing blood samples was done routinely for all cases with normal labour and for those with abruption for baseline assessment of haematocrit, renal function, and coagulation profile added to our study investigation for thyroid function, no known serious consequences of blood sampling, but discomfort, bruising and bleeding were all minor complications. Five ml of blood obtained by venepuncture, dispensed in to a plain tube, and left for 15 minutes at 4C to clot. Then, it was centrifuged at 3000 rpm for 10 minutes to collect serum. Thyroid function test (T3, T4, free T4 and TSH) were determined using commercially available Minividas kits (*biomerieux*, France), Minividas was performed according to manufacturer instructions. The normal value for T3 was (0.95-2.23), T4 (60-120) and TSH (0.25-5) µIU/ml and freeT4 (0.76-2.24). Those who had high TSH and low T3&/T4 when compared to laboratory specific normal values, were diagnosed as clinical (overt) hypothyroidism, those who had high TSH but normal freeT4 thyroid hormone were diagnosed to have subclinical hypothyroidism (SH), those in whom all hormone values were within normal limits were designated as euthyroid.

Statistical analysis:

   These were used to accept or reject the statistical hypotheses, they include the followings: ANOVA test (F-test) and (chi square test). The comparison of significant (P-value) in any test were S= Significant difference (P≤ 0.05). NS=Non Significant difference (P>0.05). All the statistical analysis was done by using Pentium-4 computer through the SPSS program   (version-14).

Results:

Figure1: illustrates the number of subclinical hypothyroidism(SH) in both control and placental abruption groups.
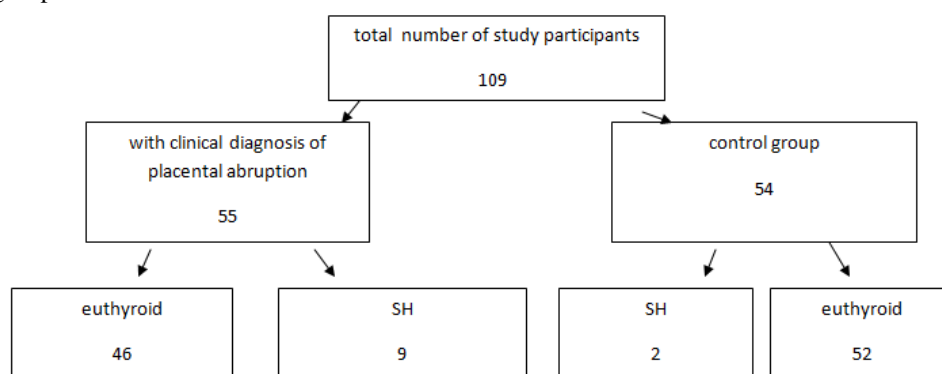
▪mean TSH for cases diagnosed with SH is 5.38±0.72, mean free T4 1.75±0.33

Table (1): Number of patients found to have subclinical hypothyroidism in both control and placental abruption groups.

Group	abruption	control	P – value
Subclinical hypothyroidism	9(16.3)	2(3.70)	P – value = 0.05
Euthyroid	46	52	chi square =3.844
Total	55	54	

Table (2): Mean of maternal age ±standard deviation for both control and placental abruption groups

Group	NO.	Mean	Std. Deviation	F-Test	P-Value
Placental abruption	55	27.49	6.58	0.141	0.708
Control	54	27.92	5.42		
Total	109	27.70	6.01		

Table (3): parity of women in both control and PA groups.

Group	NO.	0-2	3≥	Chi square Test	P-Value
Placental abruption	55	51	4	7.834	0.09
Control	54	47	7		
Total	109	98	11		

Table (4) residence of women in both control and PA.

Group	NO.	Urban	Rural	Chi square Test	P-Value
Placental abruption	55	42	13	0.169	0.681
Control	54	43	11		
Total	109	85	24		

Table (5): mean gestational age in cases of placental abruption compared to control group

Group	NO.	Mean	Std. Deviation	F-Test	P-Value
Placental abruption	55	34.67	3.39	32.579	0.001
Control	54	*37.57*	1.57		
Total	109	36.11	3.01		

Figure (2): Maternal age distribution for both cases of placental abruption and control, the difference does not reach statistical significance.
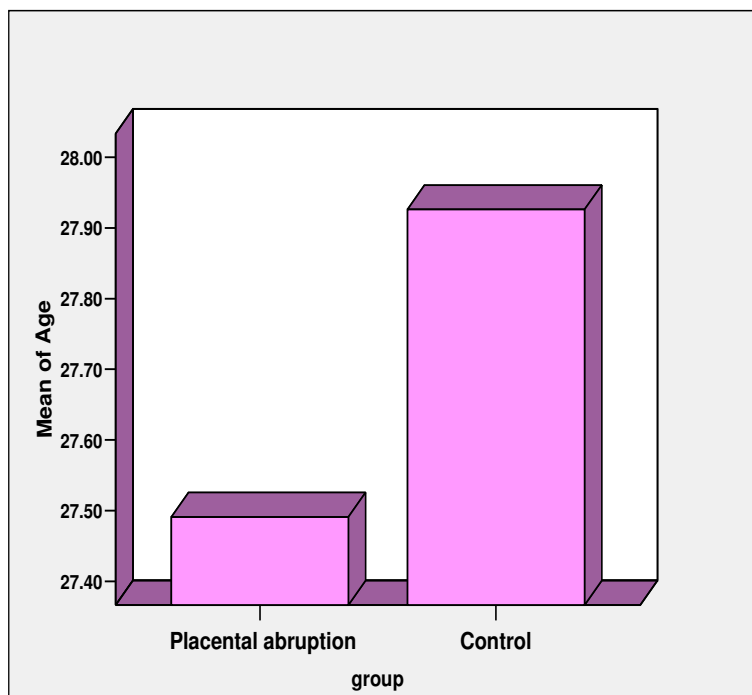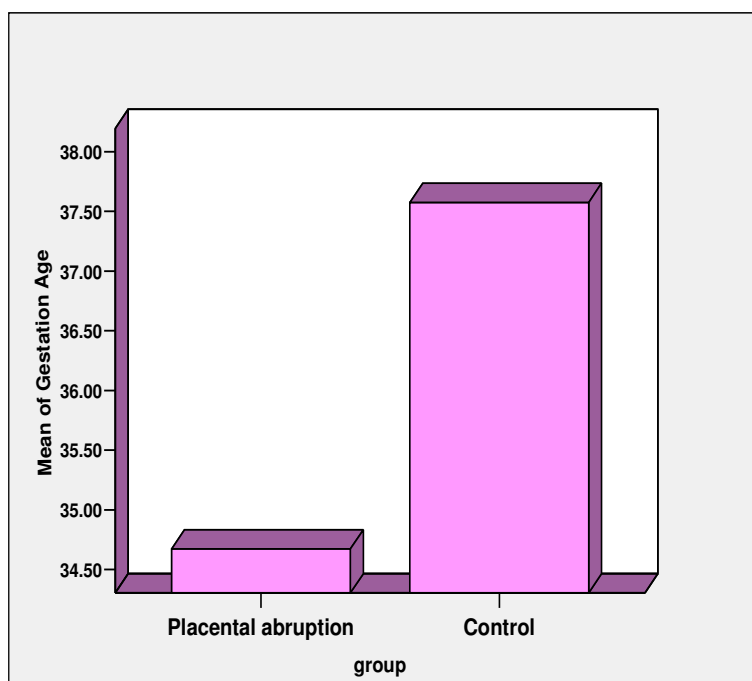

Figure (3):There is statistically significant younger gestational age for placental abruption cases than control group.

Table(6): number of cases of PA affected by SH at term and preterm gestational age.

Group of placental abruption	Abruption at term	Abruption at preterm (GA)	P – value
Subclinical hypothyroidism	3(17.6%)	6(15.78%)	P – value = 0.663
Euthyroid	14	33	chi square = 0.190
Total	17	38	

Discussion

Thyroid dysfunction is the most common endocrinological disorder affecting women of child-bearing age, and typically manifests during reproductive years, with more than half of those cases being undiagnosed. While both thyroid dysfunctions are important, the state of hypothyroidism is considered to be the more serious regarding pregnancy[21].

The important finding in this prospective cross-sectional case controlled study are first: subclinical hypothyroidism was identified in 3.7% of the control population tested, and this

corresponds with virtually all previous reports of subclinical hypothyroidism has a prevalence of 2% to 5% in pregnant women.[3,22, 23,24],however, this ratio increased to 16.3%, 9/55 (nearly fourfold) of cases diagnosed with clinical abruption as it was explained in table (1), a figure which was statistically significant and even higher than reviewed in previous reports with stated association of 2-3 fold rise incidence of placental abruption with subclinical hypothyroidism. [25, 26, 3]

Casey and colleagues studied pregnancy complications with SH, Subjects who met SH criteria were (2.3%) Their pregnancy outcomes were compared with those of control subjects with a TSH in normal ranges, researchers found no differences in gestational hypertension, preeclampsia, birth weight, or in fetal or neonatal death. Significantly more placental abruptions (relative risk [RR], 3.0; 95% CI, 1.1-8.2), were found in the SH group.[3]Cleary-

Goldman and colleagues reported on a series of subjects who were a subset of the First and Second Trimester Evaluation of Risk (FASTER) trial, in this trial, the researchers found no increased risk of placental abruption, and other adverse pregnancy outcomes. [27]

It is unclear why this large retrospective screening study reported such different conclusion.

the mechanism of disease whereby thyroid hormone deficiency leads to placental abruption, and other pregnancy complications is not known. One unifying hypothesis is that thyroid hormone is necessary for normal placental development. Specifically, there is evidence that preterm delivery and vascular diseases such as preeclampsia and placental abruption may be causally linked to faulty early placentation.[3]

Unlike Brian M. Casey, who found that women with subclinical hypothyroidism were significantly older than control women[3], in our study there was no statistically significant difference in mean maternal age among those cases of placental abruption (27.49±6.58) and control group(27.92±5.42) as was shown in table(2),

Table (3) demonstrates that most of participant women were of low parity P0-2 were 98 out of total 109 and there was no statistical difference in parity between control and PA groups(P= 0.09), this can be explained on cultural bases that most multiparous women prefer home delivery by midwife rather than to be delivered at hospital, residence as well has no statistical significant differences in both control and PA group(P= 0.681) and majority of women 85 out of109 were urban as shown in table (4), however; mean gestational age for cases of placental abruption in general was 34.67 and this was significantly lower than mean gestational age for control which was 37.57, but when gestational age studied in relation to placental abruption with SH as whown in table (6) it was found that although 6 of38 (15.78%) cases of placental abruption who were affected by subclinical hypothyroidism were at preterm gestational age and (17.6%) of PA at term this did not reach statistical significance with P value of 0.663.

Conclusion

1-SH is not uncommon condition among our laboring population

2-SH was found to increase fourfold risk of placental abruption in this study

3-maternal age was insignificant confounder between control and PA group

4- placental abruption tends to occur more frequently at preterm gestational age but this failed to reach statistical significance for cases with SH between term and preterm.

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