# The therapeutic outcome of L- carnitine in the management of thyrotoxicosis in pregnant women.

Salah kadim muslim*

*MB Ch B , fellow of Iraqi committee of medical specialization (FICMS) , colleague of arab board of surgery CABS; general surgeon, Basra general hospital. Lecturer in department of clinical pharmacy , college of pharmacy. university of Basra. Salah.kadim@gmail.com

## ملخص لبحث

تسمم الغدة الدرقية من امراض الغدد الصماء الشائعة وتكثر عند النساء وممكن ان تظهر اعراضها اثناء الحمل. ظهور المرض خلال الحمل يحمل الكثير من الاخطار على المريضة وعلى الجنين. وهذه الاخطار تتناسب طرديا مع قدرة الطرق العلاجية على السيطرة حيث ان عدم السيطرة الكاملة ممكن ان تؤدي الى مضاعفات كثيرة وكبيرة منها ارتفاع ضغط الدم اثناء الحمل، عجز القلب، الاسقاط، ولادة مبكرة بالإضافة الى تشوهات ولادية للجنين وتكون هذه اما بسبب المرض او بسبب الطرق العلاجية المتبعة.

الطرق العلاجية المتبعة هي اما العلاج الدوائي بمادة (بروبايل ثايو يراسيل) propylthio uracil او التداخل الجراحي. في العراق بشكل عام وفي محافظة البصرة بشكل خاص يصعب الحصول على هذا العقار بالإضافة الى التكلفة العالية مما يضطرنا الى اللجوء الى الخيار الجراحي والذي يحمل الكثير من المضاعفات على الام و الجنين.

مادة L-Carnitine هي من الامينات الرباعية وتلعب دورا كبيرا في الايض وتعمل على منع دخول هرمون الثروكسين الى الخلية ومن ثم تثبيط عمل الثيروكسين على كافة خلايا الجسم بالإضافة الى عدم امتلاكه اي تأثير تشوهي على الجنين ..... هذه المميزات ممكن ان تساعد في علاج مرض تسمم الغدة الدرقية اثناء الحمل.

**هدف البحث:** تقييم التأثير العلاجي من اعطاء المريض دواء L-carnitine بجرعة 4 غرام يوميا لمريضات يعانين من مرض تسمم الغدة الدرقية اثناء الحمل.

**النتائج:** تم اعطاء هذا العقار الى واحد وثلاثون امرأة , 19 حامل و12 غير حامل وبجرعة 4 غرام يوميا وتمت متابعة استجابة المريضة من خلال العلامات السريرية والتحاليل كل 1.5-2 شهر ومن خلال مدى التزام المريضة بالعلاج الموصوف.

وكانت النتائج كالاتي:

ان ثلاثة (حوالي 16%) من الحوامل لم تستجب للعلاج مما ادى الى قطع مبكر للعلاج بينما لم تستجب مريضة غير حامل للعلاج (8%). وتم التعامل مع مثل هذه الحالات هي زيادة جرعة الدواء الى 6 غرام يوميا مع او بدون اضافة عقار (البوبرانولول ) لمعالجة اعراض المرض.

عند النساء اللواتي استجبن للعلاج نجد ان ارتفاع واضح في الهرمون المحفز للغدة الدرقية TSH بينما لم يتأثر مستوى هرموني الغدة الدرقية T4 , T3. كما نجد تحسن ملحوظ في النبض لكلا المجموعتين مع العلم ان التحسن أكبر عند الحوامل.

هناك نسبة كبيرة من المجموعتين بالرغم من استجابتهن للعلاج بدأن يعانين من ارتفاع سعره مما يؤثر سلبا على التزام المريض بالعلاج المعني.

وكمحصلة للبحث نجد ان مادة L-carnitine ممكن ان تكون مادة بديلة وناجحة لعلاج تسمم الغدة الدرقية وخصوصا اثناء الحمل حيث تتضيق الخيارات العلاجية. مع هذا نجد ان ارتفاع ثمن العقار ممكن ان يكون عائقا امام استعماله بشكل اوسع.

## Summary

**Objectives:**

thyrotoxicosis during pregnancy is not uncommon condition and difficult to be treated due to lack of availability and the expense of the available medication .L.carnitine may have a promising role in the management.

**Method:**

A prospective study of thirty one women ; nineteen of them are pregnant and the remaining are not. All patients were prescribed L –carnitine 4g/day as a management for their thyroid problem. After 1.5-2 months; re-evaluation is done to all patients regarding clinical and laboratory response. Patient compliance and side effects of the medication were monitored in each follow up visit. For non-compliant patients; the causes of non-compliance were identified.

**Results**

A three ( 15.8%) pregnant women showed a poor responded to 4g / day of L-carnitine with their Thyroid function test and heart rate did not improved by the treatment; therefor the dose of L- carnitine increased to 6 g daily with or without addition of propranolol daily orally to minimize symptoms of hyperthyroidism especially heart rate .In the non-pregnant group; only one woman (8.3%) are not responded to the treatment.

Regarding the changes in the thyroid function test; both groups showed significant increase in TSH while both showed insignificant changes in free T3and T4.

Most patients in both groups were complained from the high cost of therapy, which may decrease the adherence of patients to the treatment and resulted in discontinuation of therapy in some patients and the preference to thyroidectomy in others.

**Conclusion:**

The addition of 2-4 grams of oral L-carnitine daily is an effective tool for reducing symptoms of thyrotoxicosis. It could be used alone or in conjunction with anti-thyroid drugs or alternative medicine, so L-carnitine is considered as welcomed addition for the management of hyperthyroidism.


Keywords: hyperthyroidism, thyroidectomy, thioamides, propylthiouracil, methimazole, carbimazole; L –carnitine

**Introduction:**

Thyroid storm is rare in pregnancy, but hyperthyroidism is not; especially Graves' disease, which is the commonest type of hyperthyroidism in pregnancy and it represents about 85% of all causes of hyperthyroidism in pregnancy [1] Maternal hyperthyroidism is associated with an increased risk of pre-eclampsia, maternal heart failure, spontaneous abortion or fetal loss, preterm delivery, stillbirth and low birth weight.[2] The risk of complications for both the mother and the fetus is related to the duration and control of maternal hyperthyroidism. In addition; poor control of hyperthyroidism during gestation has been associated with congenital malformations unrelated to anti thyroid drugs ingestion. [3] [4] And; it may lead to loss of fetus or the mother.[5]

In pregnancy; Generally thioamides are consider as only rational non-surgical choice; to control excessive secretions of thyroid hormones in pregnant women, and Propylthiouracil is the thioamide of choice in pregnancy [6]. Since methimazole or carbimazole use was with precautions; due to their association with some fetal teratogenicity such as

aplasia cutis; a congenital absence of skin on the fetal scalp. [7], and choanal or oesophageal atresia [8]. In addition to that; thioamides could cross placenta and may cause fetal hypothyroidism [9] .

In Iraq, especially in basrah city; propylthiouracil is not always available! So surgical option or the cost of obtaining the drugs from outside the country is the only method used to treat such cases.

The surgical option (thyroidectomy) is not regarded as first-line therapy, due to obstetric and fetal risks, but might be considered if necessary. In practice; surgery during the first trimester has been associated with an increased rate of spontaneous abortions. If possible, therefore, surgery should be delayed to the second trimester. [10] Although surgical termination of pregnancy may have additional risk of life threatening thyroid storm. [11] therefore; thyroidectomy is indicated when:

- ✓ There is requirement for continued large doses of antithyroid drugs (propylthiouracil >450 mg), or hypersensitivity reactions or intolerance to drug therapy.
- ✓ goiter causing symptoms of dysphagia or airway obstruction,

So therapeutic strategies, and, even diagnostic procedures, are restricted by an absolute need to avoid radio-isotopes, to avoid surgery if possible and to minimize the risk of other iatrogenic harm during pregnancy

L-carnitine is a quaternary amine (hydroxy--trimethylammonium butyrate) that is ubiquitous in biological fluids and tissues of mammals, where it plays an important role in energy metabolism [12]. Carnitine may inhibit thyroid hormones entry into the nucleus of human and animal cells (fibroblasts, hepatocytes, neurons), which explain its peripheral antagonism activity for thyroid hormones.[13] thus L-carnitine may be an interesting chemical to be used in management of such condition in pregnancy; because it is endogenous substance and may lack teratogenic effect.

**Aim of study**

Evaluation the therapeutic outcomes of L carnitine 4g/ day, as alternative option for thioamides & surgery (thyroidectomy) in pregnant women with hyperthyroidism.

**Patients & methods**

A prospective study of thirty one female patients diagnosed as having thyrotoxicosis depending on the clinical features, thyroid function test and neck ultrasound. Twelve of them were non pregnant and nineteen pregnant women. Verbal consent was obtained from all participants and all patients were prescribed L –carnitine 4g/day as a management for their thyroid problem.

Patient response to treatment was revaluated after(1.5-2) months following the treatment . It consist of clinical improvement in her symptoms of nervousness , irritability , heat intolerance ; decreasing the heart rate and rise in the serum level of TSH and decrease in free T4, T3.

Patient compliance and side effects of the medication were monitored in each follow up visit. For non-compliant patients; the causes of non-compliance were identified.

Data analysis was performed using Microsoft excel,2010; and the data analyzed using *t*- test and simple descriptive statistics

**Results**

The mean age was (26.4 + 1.9 years) for non-pregnant women and (28.8 + 1.9 years) for pregnant women group. There was no significant difference ($p<0.05$) of age between both groups.

Table(1) shows the percent of patients with poor response and prematurely discontinued the treatment. There were (15.8% , N=3) of pregnant women are poorly responded to 4g / day of L-carnitine with their Thyroid function test and heart rate did not improved by the treatment; therefor the dose of L-carnitine increased to 6 g daily with or without addition of propranolol daily orally to minimize symptoms of hyperthyroidism especially heart rate .In the non-pregnant group; the incidence of such condition was less, and was (8.3% , N=1).

Most patients in both groups (84.2% , N= 16 ) of pregnant and ( 91.7% , N=11 ) of non-pregnant were complaining from high cost of therapy, such complaining may negatively affect adherence of patients to the treatment and resulted in discontinuation of therapy by (25% , N=3) of non-pregnant and (10.52%, N=2) of pregnant where those patients preferred thyroidectomy after the second visit. See figure 1.

Total No. of In table 2; serum TSH was significantly ($p<0.05$) elevated, for both

**Table 1** Shows percent of incidence of patients poor compliance ,treatment discontinuation and cost complaining for both pregnant & non pregnant groups of patients after 1.5-2 month(s) treatment with 4g daily of L-carnitine

| | Total No. of subjects | No. of poorly respond for 4 gram/day L- carnitine | | Prematurely discontinue treatment (prefer surgery) | | Complaining from cost | |
|---|---|---|---|---|---|---|---|
| Pregnant | 19 | 3 | 15.8% | 2 | 10.52% | 16 | 84.2% |
| Non pregnant | 12 | 1 | 8.3% | 3 | 25% | 11 | 91.7% |

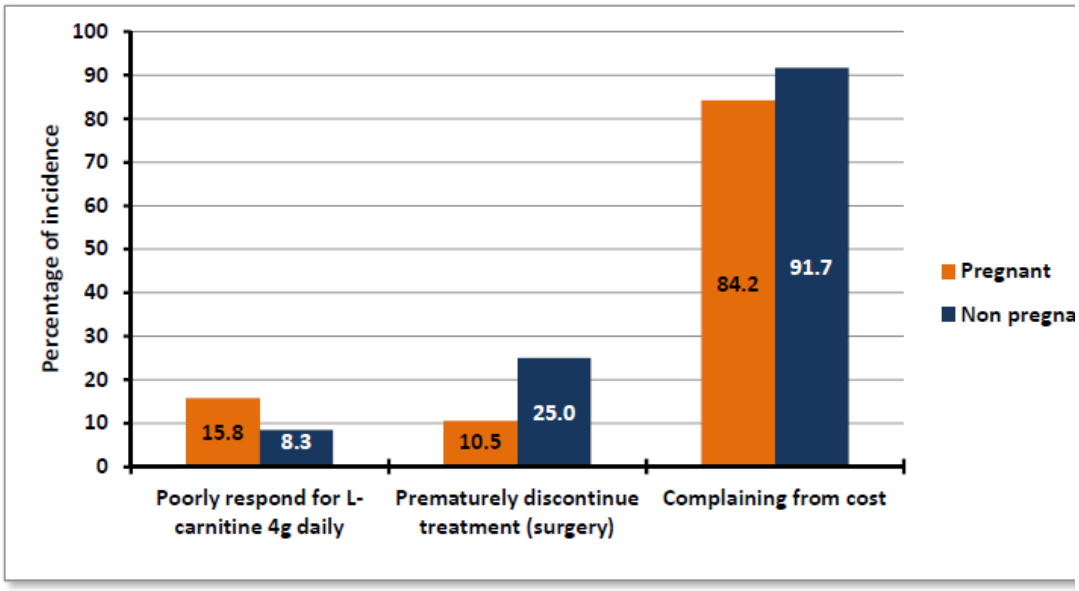


**Figure 1** histogram shows of incidence ratios of poor response, cost complaints and premature discontinuation of therapy with 4g/day L- carnitine

groups, as compared with pretreatment values. (from 0.029 + 0.004 mIU/L to 0.79 + 0.17 for pregnants & from 0.022 + 0.002 mIU/L to 0.34 + 0.05 mIU/L for non pregnants). The elevation of serum TSH level, after treatment, was significantly (at $p<0.05$) greater in pregnant women group (0.79 + 0.17 mIU/L for pregnant vs. 0.34 + 0.05 mIU/L for non-pregnant).

For serum T4, T3 both groups show no significantly (at $p<0.05$) changes as compared with before treatment values, and there were no significant (at $p<0.05$) differences between both groups. Heart rate, was significantly (at $p<0.05$) lowered after treatment in both groups, (from 114.3 + 4.5 ) to( 92 + 4.9) Beats per minute for pregnant and from( 109.7 + 2.1) to( 77.8 + 2.5) Beats per minute for non-pregnant. But the heart rate remained significantly (at $p<0.05$) higher after treatment in pregnant group as compared with non-pregnant (92 + 4.9 Beats per minute for pregnant vs. 77.8 + 2.5 Beats per minute for non-pregnant). See figures (2-5).

**Table 2** Shows differences in thyroid function test parameters and heart rate before & 1.5-2 month(s) after treatment with L- carnitine 4g/day; data expressed as mean +/- Standard error of mean

| | | Pre-treatment | | | After treatment | | | |
|---|---|---|---|---|---|---|---|---|
| pregnant | TSH (mIU/L) | 0.029 | ± | 0.004 | 0.79 | ± | 0.17 | * |
| N=19 | T4 (µg/dl) | 200.5 | ± | 17.1 | 208.3 | ± | 4.7 | |
| | T3 (ng/dl) | 2.05 | ± | 0.2 | 2.07 | ± | 0.08 | |
| Age: 28.8 ± 1.9 years | Heart rate | 114.3 | ± | 4.5 | 92.0 | ± | 4.9 | * |
| Non pregnant | TSH (mIU/L) | 0.022 | ± | 0.002 | 0.34 | ± | 0.05 | *a |
| N=12 | T4 (µg/dl) | 207.5 | ± | 15.5 | 192.5 | ± | 10.6 | |
| | T3 (ng/dl) | 2.09 | ± | 0.11 | 2.02 | ± | 0.12 | |
| Age: 26.4 ± 1.9 years | Heart rate | 109.7 | ± | 2.1 | 77.8 | ± | 2.5 | *a |

* significant at($p<0.05$) as compared with pre-treatment values

a significant at($p<0.05$) as compared with pregnant values

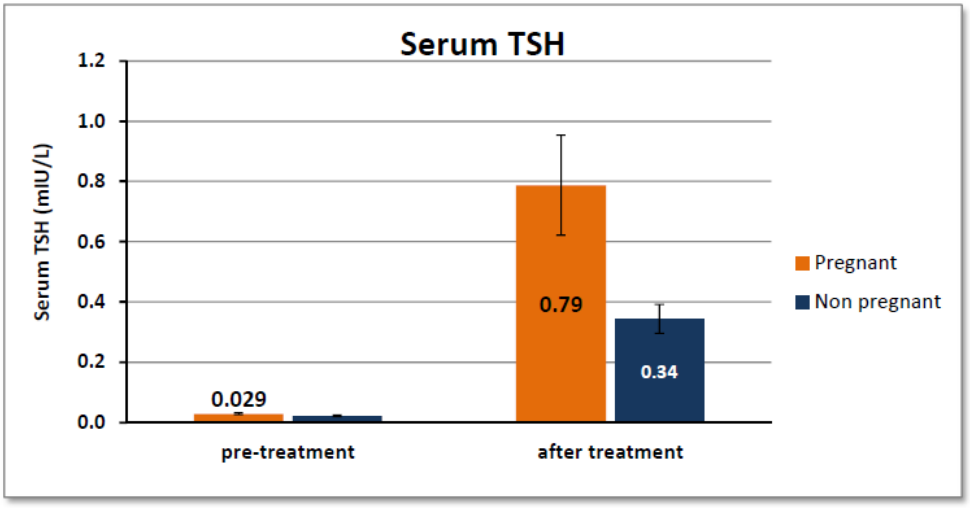


**Figure 2** Histogram shows difference in serum level of TSH before and 1.5-2month(s) after treatment with 4g daily of L carnitine for both pregnant and non pregnant group of patients

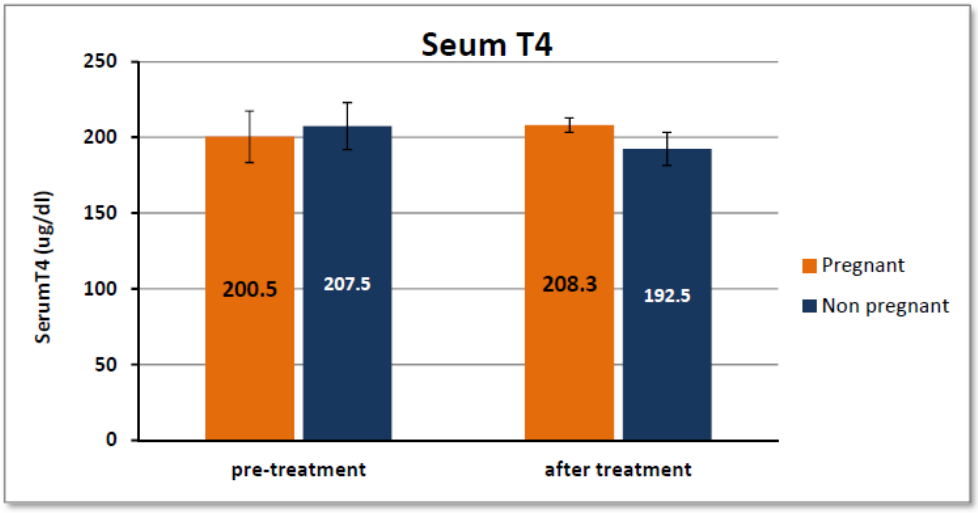


**Figure 3** Histogram shows serum level of T4 before and 1.5-2month(s) after treatment with 4g daily of L carnitine for both pregnant and non pregnant women group of patients

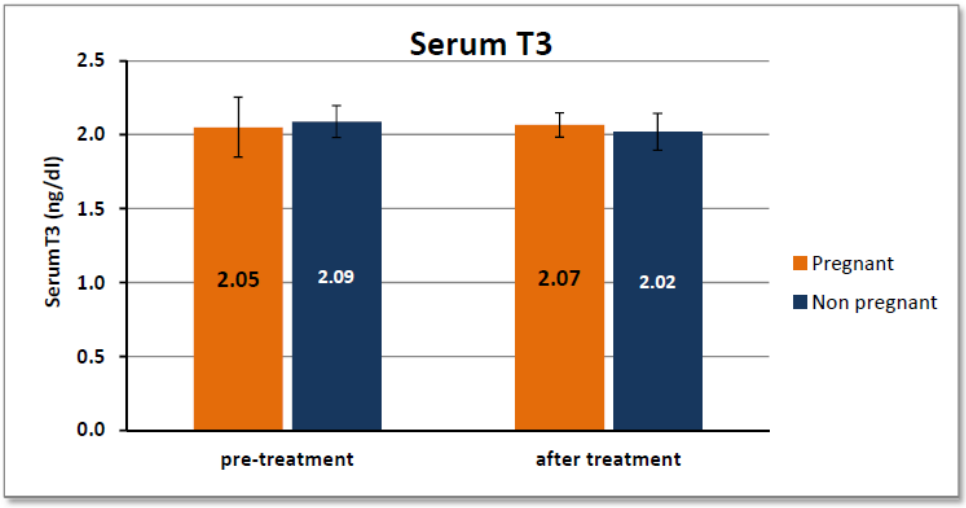


**Figure 4** Histogram shows serum level of T3 before and 1.5-2month(s) after treatment with 4g daily of L carnitine for both pregnant and non pregnant women group of patients

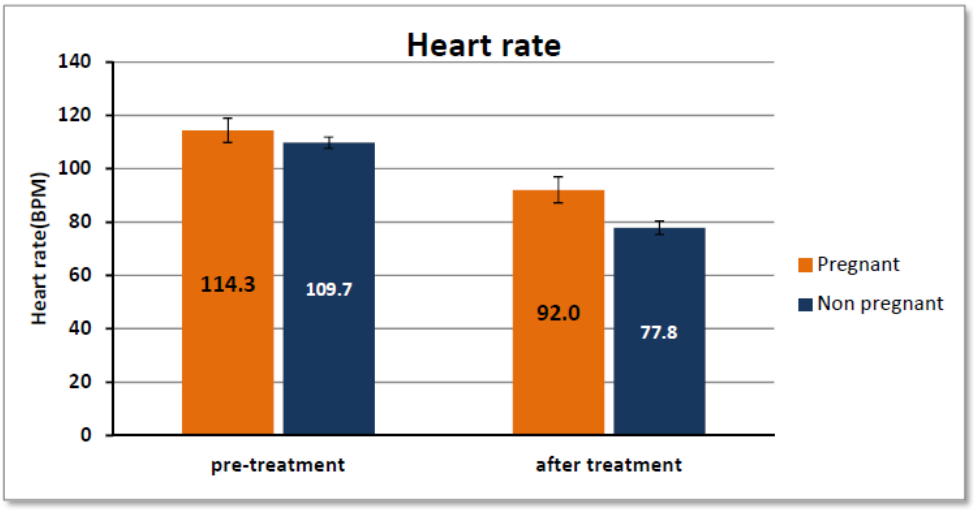


**Figure 5** Histogram shows lowering in heart rate before and 1.5-2 month(s) after treatment with 4g daily of L carnitine for both pregnant and non pregnant women group of patients

**Discussion**:

L-carnitine is quaternary amine which is synthesized in vivo from lysine and methionine in the kidney and liver of all mammals. L-carnitine is metabolically used for the transport of long chain fatty acids from the cytosol into the mitochondrial matrix for β-oxidation [14]. In humans, the liver and the kidneys synthesize 25% of L-carnitine used in the body; the remaining 75% is supplied by diet [15] .In hyperthyroidism; L-carnitine and other nutrients are depleted from the body, so supplement of L-carnitine is rational and dose as high as 4 grams daily are found not associated with toxicity and teratogenicity (effects on offspring), [15;16,19] . Overall, studies results show that the addition of 2-4 grams of oral L-carnitine daily is an effective tool for reducing symptoms of nervousness, heat intolerance, insomnia, emotional instability, tremors, and excessive sweating in hyperthyroidism. It could be used alone or in conjunction with anti-thyroid drugs or alternative medicine, so L-carnitine is considered as welcomed addition for the management of hyperthyroidism. [16]

*In table 1.* There is significant ($p<0.05$) elevation in ratio of patients poor responseto the prescribed dose of l-carntine (4 gm/day) among pregnant women as compared to non-pregnant (15.8% Versus 8.3%); Although the patients were sticky to prescribed dose of the drug as they confirmed. This finding may be explained by physiological changes accompanied pregnancy like elevated HCG which may further worsen thyroid status; since it may act as thyroid stimulator and mimic the activity of TSH [17], or development of anemia due to plasma expansion, and increase iron requirement and accompanied increase in heart rate and cardiac output [18]. Also, the presence of infection such as urinary tract infection, which is common in pregnancy, may worsen symptoms of hyperthyroidism. These patients may benefit from the addition of propranolol with or without increase dose of L carnitine to 6 g/day.

Most of patients on L- carnitine complaining from its cost (84.2% for pregnant and 91.7% for non-pregnant) , which is approximately 3000 Iraqi dinars per daily dose and this could be considered as the major cause behind the lack of long term use, probably in Iraq.

These finding is reverse to the findings reported by (Salvatore Benvenga *et. al.*; 2001), where he state that ( 79-85 % of

patients preferred to continue on l-carnitine for long term use)[16].

In this study , early discontinuation of treatment and preference of surgery or other drug treatment is more frequent in non-pregnant than pregnant women group (25% versus 10.52% for pregnant); this may be related to the fear of pregnant women from adverse events of surgery , and unavailability of safe alternative drug treatment during pregnancy.

In table2; before treatment with L-carnitine 4g/day, serum level of TSH was lower than normal value (0.4 - 4.0 mIU/L [20]) in both groups (0.029+ 0.004 mIU/L for pregnant vs. 0.022+ 0.002 mIU/L for non-pregnant), which is consistent biochemical finding in hyperthyroidism [20]. After treatment ; TSH is significantly ($p<0.05$) elevated (0.79 + 0.17 mIU/L for pregnant and 0.34 + 0.05 mIU/L for non-pregnant women). This is may be related to blockade of T3& T4 nuclear receptors [13] that may reduce or abolish inhibitory effect of excess thyroid hormones on hypothalamus pituitary axis resulting in resumption of TSH secretion from anterior pituitary gland. This finding may be reverse to that reported by (Salvatore Benvenga *et. al.*; 2001) in their pilot study; where they state that; (carnitine does not antagonize the physiological negative feedback of thyroid hormones on TSH secretion.)[16] . Also after treatment, the elevation in serum TSH was significantly ($p<0.05$) greater in pregnant than non-pregnant (0.79 + 0.17 mIU/L for pregnant vs. 0.34 + 0.05 mIU/L for non-pregnant women); the causes behind this finding are unknown.

Levels of T3 & T4 were not significantly ($p<0.05$) changed after treatment with L-carnitine in both groups of study; and there was no significant differences between two groups of the study. this may differ from that reported by some researches who reported that L-carnitine may lead to increase level of circulating T3 and T4 [22,23]. This may be related to action of L- carnitine as T3 & T4 receptor blocker. [21] Where it does not interfere with thyroid hormone synthesis and release[24, 25].

Heart Rate was significantly ($P<0.05$) reduced after treatment with L-carnitine in both groups; Which consistent with that reported by other researcher like (Salvatore Benvenga *et. al.*; 2001). Heart rate in pregnant women group, after treatment with L-carnitine, remained significantly ($p<0.05$) higher than in non-pregnant women, this may obey the physiological changes during pregnancy [18] .

**Conclusions:**

L-carnitine 4gm/day is probably useful alternative drug management for thyrotoxicosis in female pregnant ;as alternative to other thyrotoxicosis managements, at least during the period of pregnancy. In some circumstances the dose of L-carnitine can be increased to 6gm/day in order to achieve the therapeutic outcome. Also Propranolol ,sometimes in selected cases, is required during pregnancy to control heart in addition to L-carnitine. The major Problem with L-carnitine is high cost.

Measuring of TSH level could be only meaningful biochemical marker to monitor the response to L-carnitine.

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