SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Endocrinology

Hyperthyroidism and Pregnancy

Sara Ijdda[1*], S. Rafi[1], G.H. Elmghari[1], N. El Ansari[1]

[1]Department of Endocrinology, Metabolic Diseases, Diabetology and Nutrition, Arrazi Hospital, Mohammed VI University Hospital, Faculty of Medicine and Pharmacy of Marrakech, Cadi Ayad University, Marrakech, Morocco

DOI: 10.36347/sasjm.2023.v09i10.001 | **Received:** 18.06.2023 | **Accepted:** 23.07.2023 | **Published:** 03.10.2023

***Corresponding author:** Sara Ijdda
Department of Endocrinology, Metabolic Diseases, Diabetology and Nutrition, Arrazi Hospital, Mohammed VI University Hospital, Faculty of Medicine and Pharmacy of Marrakech, Cadi Ayad University, Marrakech, Morocco

Abstract **Original Research Article**

***Introduction*:** Hyperthyroidism in pregnancy is defined by low TSH, below the specific reference values of each trimester with high levels of free T3, free T4 or both. Source of serious complications for both the mother and the fetus. The aim of our study is to determine the clinical, paraclinical, etiological and therapeutic aspects. ***Material and Methods*:** We have collected in this work the cases of hyperthyroidism duringpregnancy encountered in the endocrinology, maternal intensive care and gynecology departments of the Marrakech University Hospital. ***Results*:** we have collected 32 cases of hyperthyroidism during pregnancy. The average age was 29 years old. Functional signs were dominated by uncontrollable vomiting and weight loss. As for the thyroid assessment, the average TSH level was 0.017 with an average T4 level of 53.30 and T3 of 15.74. The etiologies were dominated by transient gestational hyperthyroidism (TGH) and Graves' disease. The management was essentially based on hydro-electrolyte rebalancing, then the etiological treatment in a second step. ***Discussion*:** Hyperthyroidism is considered to be the second endocrinopathy in pregnant women, after gestational diabetes. It would be present in 1 to 3% of pregnant women, the most common causes are Graves' disease and TGH. ***Conclusion*:** Pregnancy hyperthyroidism is a frequently encountered situation. The identification of the cause of hyperthyroidism must be established because it guides the follow-up andpregnancy care.

Keywords: Hyperthyroidism, pregnancy, complications, management.

INTRODUCTION

Pregnancy represents a challenge for the thyroid gland, which gland must ensure the increased needs in thyroid hormones, especially during the first half of gestation, when the fetal thyroid gland is still not functional, and the intake of these hormones in the fetus depend essentially on the maternal gland [1]. Thus, several physiological changes affect the maternal thyroid gland, and allow a 50% increase in the production of thyroid hormones. Pregnancy is therefore a favorable period for thyroid disorders [1]. In particular, the hyperthyroidisms in which we were interested in this study, they occur in approximately 2 to 3% of pregnancies [2].

Hyperthyroidism in pregnancy is defined by low TSH, below specific trimester reference values with high levels of free T3, free T4, or both. The etiologies are dominated by transient gestational thyrotoxicosis and Graves' disease, the other causes are exceptional [3].

Uncontrolled hyperthyroidism that persists can lead to obstetric, fetal or neonatal complications, hence the need and importance of early diagnosis and adequate treatment [4]. Initial management generally consists of symptomatic treatment with correction of hydroelectrolyte disorders [5]. However, other therapies may be considered depending on the severity of the clinical picture and the presumed etiology.

MATERIALS AND METHODS

Our study was prospective, descriptive, aiming to evaluate the prevalence of hyperthyroidism during pregnancy, its clinical, biological, etiological, therapeutic and evolutionary aspects. Including pregnant patients, hospitalized in the endocrinology, maternal intensive care and gynecology departments at the university hospital center Mohamed VI in Marrakech, presenting clinical and biological signs of hyperthyroidism, all etiologies combined; this study lasted a period of one year, from January to December 2021.

For each patient, an evaluation of the circumstances of discovery was carried out, the anthropometric parameters, positive diagnosis and etiology were collected, as well as the therapeutic approach and the follow-up. The collection of clinical data was carried out using an exploitation sheet.

Outcomes:

In our sample of 32 patients with hyperthyroidism during pregnancy, the average age was 29 years with extreme ages ranging from 19 to 44 years. We studied the distribution of our patients according to 4 age groups.

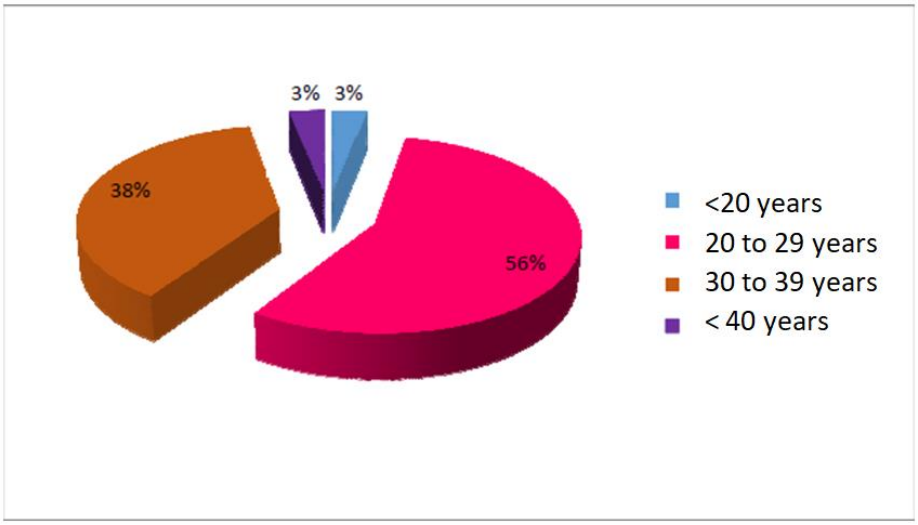

Figure 1: Distribution of cases according to age groups

In 37.5% (N=12) of our patients, it was their first pregnancy. The average gesture rate is 2.53 gestures with a maximum of 7 gestures and a minimum of one gesture. The average parity ranged from 0 to 6 parities.

As for fetal and neonatal mortality, 7 patients had a history of miscarriage (21.8%); 2 patients had a history of fetal death in utero (6.25%) and 2 patients had a history of neonatal death (6.25%).

The average gestational age of our patients was 13.38 weeks of amenorrhea; 75% of our patients were in the first trimester.

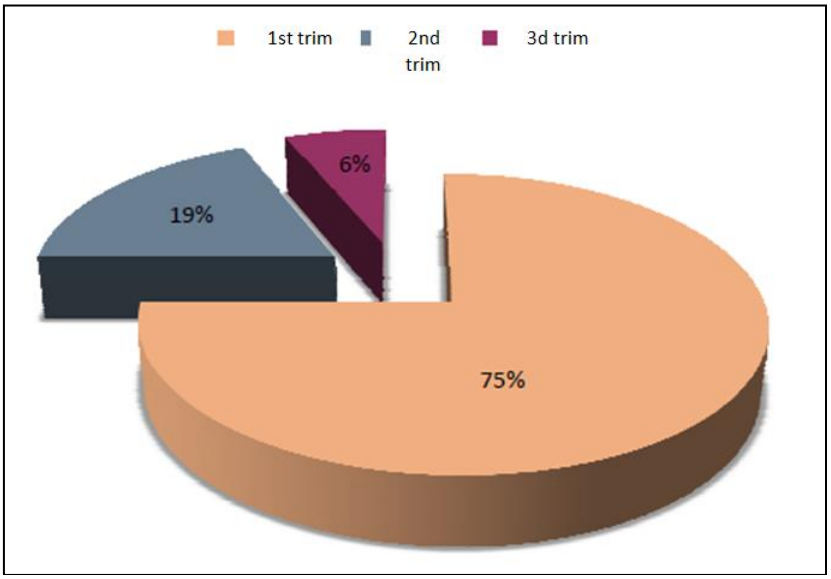

Figure 2: Distribution of cases by gestational term

Signs of hyperthyroidism prior to pregnancy were present in 7 patients (21.8%). Concerning the functional signs, out of the 32 patients, 30 presented uncontrollable vomiting at an average rate of 8 episodes/day (93.75%), and 27 presented significant weight loss (84.37%). The other signs were distributed as follows:

- Asthenia (31.25%).
- Palpitation (31.25%).
- Thermophobia (18.75%).

- Insomnia (9.37%).
- Nervousness (6.25%).
- Tremor (3.125%).

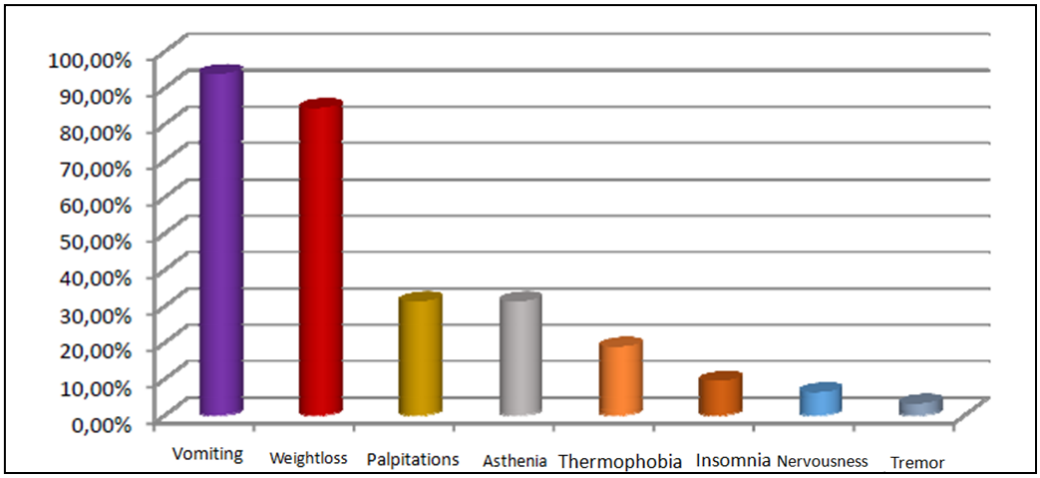

Figure 3: Distribution of clinical signs

The average heart rate of our patients was 98 from the extremes of 65 to 139 beats per minute. Tachycardia was present in 50% of patients.

A beating homogeneous goiter was objectified in 25% of the patients; Cervical examination was normal in 75% of patients. Exophthalmos was present in 18.75% of patients. Dehydration was present in 65.62% of patients.

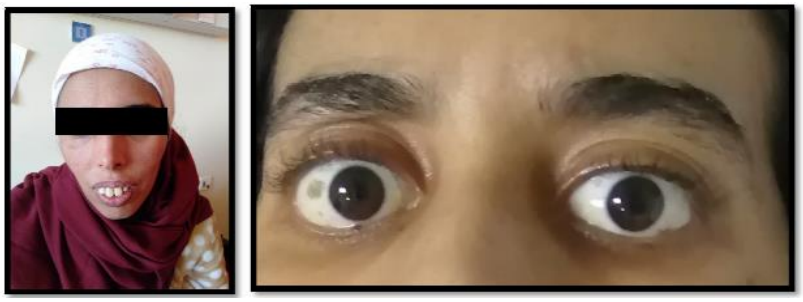

Figure 4: Two patients in our series, the one on the left presenting undernutrition with dehydration and the one on the right presenting exophthalmos

As for the paraclinical profile of our patients, the average TSH level was 0.017 with extremes of 0.005mui/l to 0.1mui/l; the mean T4 level was 53.30 with extremes of 20.6 to 100 pmol/l; the average T3 level was 15.74 with extremes of 5.3 to 50 pmol/l. The mean beta CGH (coriogonadotrophic hormone) level was 173970.2 m IU/ml.

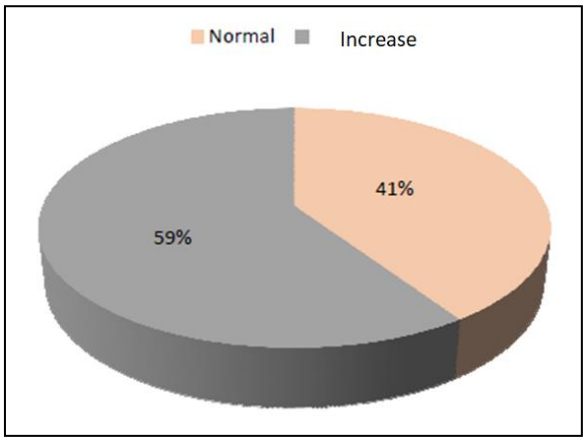

Figure 5: Distribution of cases according to Beta CGH level

Mean serum sodium was 132 mmol/l with extremes of 105 to 141 mmol/l; mean serum potassium on admission was 3.23 mmol/l with extremes of 1.66 to5mmol/l; and the functional renal insufficiency was objectified in 21.9% of patients.Hepatic cytolysis was found in 21 patients (65%).

All the patients benefited from a sample of TRab, anti TPO and anti Thyroglobuline antibodies, but unfortunately the serial processing of these assessments was not carried out given the lack of reagents at the hospital (the post-Covid period), however, 5 patients were able to perform it externally. It turned out to be negative for 4 patients, moreover the anti-TPO antibodies were positive in one patient.

Regarding the electromyogram of our patients, sinus tachycardia was noted in 14 patients (43.75%).

Cervical ultrasound was performed in 15 patients, it was abnormal in 53.33% of patients (8 cases), showing:

- Nodule in 3 women.
- Hetero-multi-nodular goiter in 4 women.
- Shrunken thyroid in a woman.

Table 1: Distribution of patients according to cervical ultrasound result (n=15)

Outcomes of cervical ultrasound	Percentage
Nodule	20%
Nodulargoiter	26.67%
Thyroiditis	6.66%

The presumption of the etiological diagnosis of hyperthyroidism was based on a bundle of epidemiological, clinical, paraclinical and evolutionary arguments. It should be noted that 4 patients were lost to follow-up.

Table 2: Distribution of patients according to the diagnosis selected

Diagnosis	Number of cases (N=28)	Percentage
Transient gestational hyperthyroidism (TGH)	12	42.85%
Basedow disease	7	25%
Toxic adenoma	3	10.72%
Thyroiditis	1	3.58%
Nodular goiter	4	14.27%
Iatrogenic hyperthyroidism (contrast agent)	1	3.58%

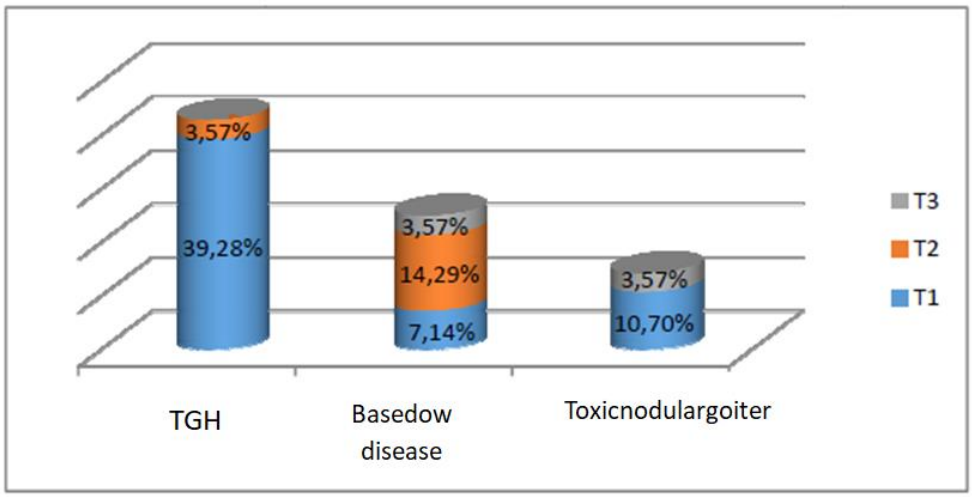

Figure 6: Distribution of cases according to the diagnosis selected and the trimester

The treatment of pregnancy-induced hyperthyroidism involved:

1. **Symptomatic Treatment**: including rest, antiemetics, proton pump inhibitors (PPI), vitamin B12 therapy.
2. **Rehydration, potassium supplementation and correction of serum sodium** based on the ionogram were performed in 59.3% (19 cases) of our patientshaving electrolyte disturbances.
3. **Synthetic Antithyroid Drugs**: treatment with synthetic antithyroid drugs (ATS) was administered to 9 patients, (32.14%), it had called on:
   - Carbimazole (CMZ) which was prescribed in 6 patients or 21.42%.
   - Methimazole which was prescribed in 3 patients or 10.72%.

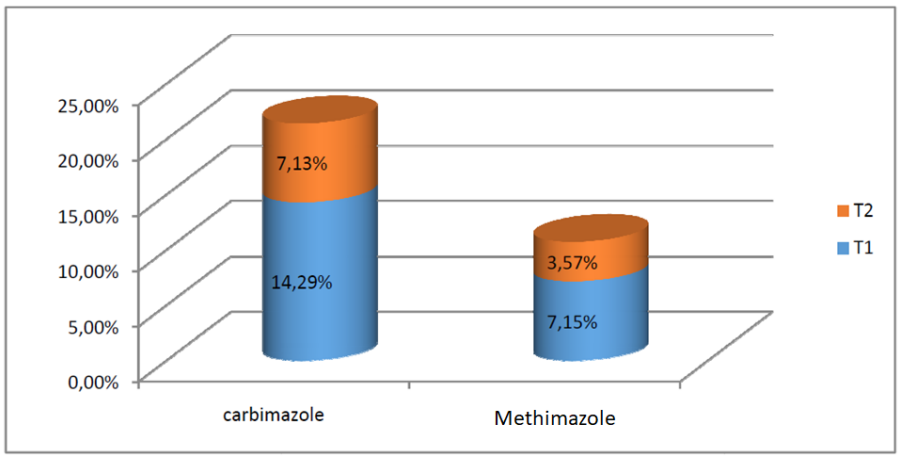

Figure 7: Distribution of cases by type of ATS and by trimester

4. **Beta blockers**: propranolol in particular, in 42.85% (12 cases).
5. **Corticosteroid therapy**: in 6 patients, (21.42%).
6. **Plasmapheresis:** in 3 patients, (10.71%).
7. **Surgery**: surgery was proposed for a patient
8. **Hemodialysis**: was indicated for one patient after correction of hypokalaemia (GFR= 4.57 ml/min/1.73m2).

Concerning the evolution of the disease, an improvement of the symptomatology with normalization of the thyroid and hepatic assessments under a symptomatic treatment alone was observed in 13 patients or 46.42%.

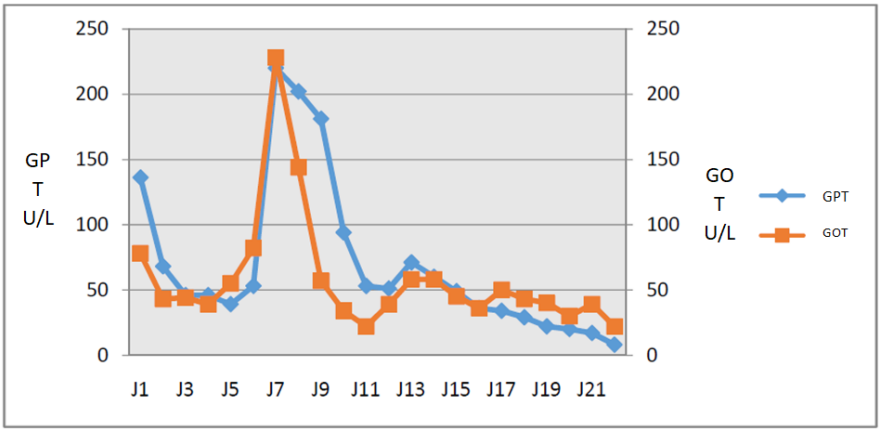

Figure 8: Normalization of liver function tests in a patient withTGT who received the symptomatic treatment alone

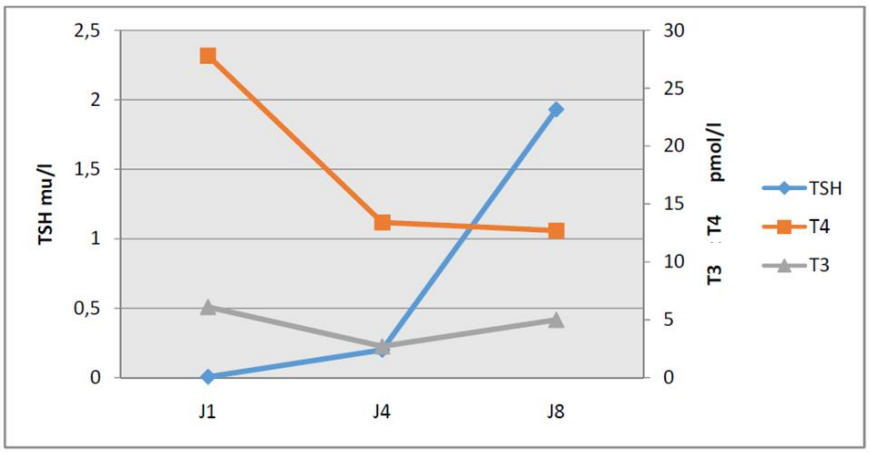

Figure 9: Evolution of the thyroid balance in the same patient also under symptomatic treatment

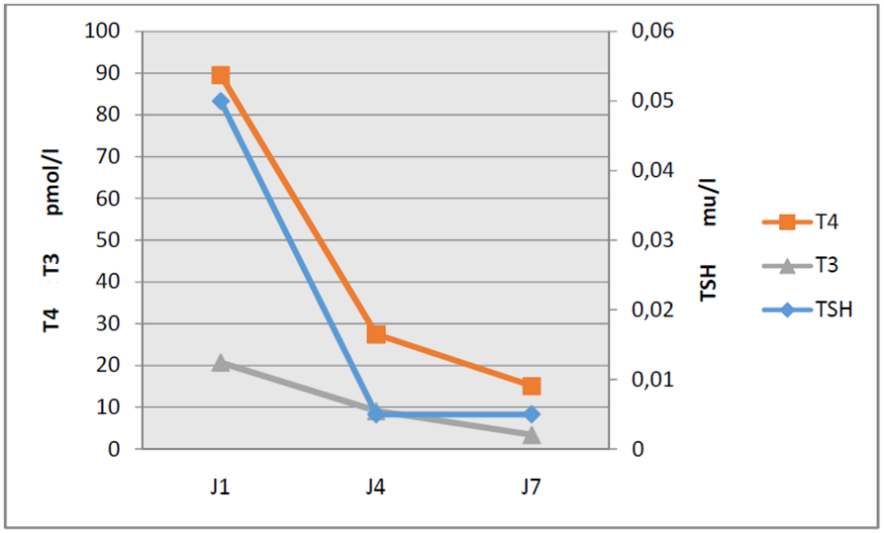

Figure 10: Improvement of thyroid status in a patient with Graves' disease put on methimazole

A woman died after being released from medical intensive care in unknown circumstances, in this case the information of the death was collected through the telephone call of our team from her husband (3.57%). Three patients had Wernicke's encephalopathy with hospitalization in the neurology department (10.71%) and one patient had hemolytic uraemic syndrome (HUS) (3.57%).

As for the evolution of pregnancy, one patient presented pre-eclampsia (3.57%), and the threat of premature delivery was noted in one patient (3.57%). Fetal death in utero was noted in 1 case, one patient had an abortion (3.57%).

DISCUSSION

Thyroid dysfunctions are highly prevalent in young women of childbearing age, and therefore dysthyroidism is common during pregnancy. Hyperthyroidism, essentially biological, is found in 1 to 3% of pregnancies. The prevalence of thyrotoxicosis during pregnancy is estimated between 0.1 and 0.4% [6-8]. The risk of occurrence of hyperthyroidism has been shown to be higher during the 1st trimester and lower during the 3rd trimester [9].

The clinical signs of hyperthyroidism are difficult to dissociate and can easily pose a diagnostic problem for the clinician because they mimic the symptomatology of early pregnancy [10]: tachycardia, emotional lability, appetite disorders, thermophobia, palpitations, digestive disorders … Two signs would be particularly evocative: the absence of weight gainor even weight loss contrasting with a preserved appetite and permanent tachycardia greater than 90 beats per minute [6, 11].

During pregnancy, due to the necessary adaptation to the specific metabolic changes of gestation, the reference intervals of the thyroid assessment are different and must be adapted for each trimester. The TSH, in connection with the increase in the CGH level, will decrease during pregnancy, in particular in the 1st trimester. Its rate increases again in the 2nd and 3rd trimester but remains below the fixed values for the non-pregnant population. The higher the CGH level, the lower the TSH: according to Lockwood *et al.*, we observe for CGH concentrations above 400,000 IU/L, a TSH level suppressed by 100% [12].

The 2011 American Thyroid Association recommendations set the following TSH thresholds [13]:

Regarding thyroid hormones, the circulating concentration of total and protein-bound T4 levels is increased from the 6-8th week, up to about 50% of its pre-gestational level and the rest throughout the duration of pregnancy [7]. The level of free T4 rises in the first trimester and then decreases throughout pregnancy due to the decrease in the expression of the thyroid hormone receptor [14].

Regarding the etiologies of hyperthyroidism, transient gestational hyperthyroidism (TGH) is the most frequent hyperthyroidism of pregnancy (2 to 3%) [15],

limited to the first trimester. It is a non-autoimmune hyperthyroidism of variable severity, which results from the thyroid-stimulating action of CGH [16].

The clinical presentation is quite variable, from the complete absence of symptoms without this disturbing the normal course of pregnancy, to uncontrollable vomiting during the 1st trimester of pregnancy. Nausea/vomiting are not symptoms of hyperthyroidism itself but are related to CGH levels [18]. The most common symptom of TGH associated with vomiting is tachycardia which results from dehydration and normalizes after hydroelectrolytic correction. There may also be fine tremors of the extremities and proximal muscle weakness.

To differentiate betweenTGH and Graves' disease, clinical examination and questioning about the patient's history and background are essential. In the absence of a history of thyroid disease, the absence of stigmata of Graves' disease, a borderline biological disorder, and symptoms of gravidarum hyperemesis, the diagnosis should be based onTGH [19], [20].

Hyperemesis gravidarum (HEG) is the most severe stage of vomiting. It presents with incoercible vomiting with a loss of weight greater than 5 kg, dehydration and the presence of fasting ketonuria. In some cases (approximately 30 to 40%), hydro-electrolyte disorders (hypokalemia, hyponatremia, metabolic alkalosis and hypochloremia) and liver function disorders can be observed (inapproximately 40-45%) [16, 17, 20]. HEG is most often benign but can also cause serious maternalcomplications such as Gayet Wernicke's encephalopathy [21]. A history of HEG can be found in previous pregnancies or in the family [6].

TGH is a frequent, moderate and transient disorder. The CGH level will decreaseduring the 1st trimester at the same time as the vomiting will improve. TSH canremain suppressed for a few more months but free T4 normalizes around the15th week [16]. Free T4 is elevated in the vast majority of cases, but free T3 is only elevated in 20 to 40% of patients [6, 17], [22]. In patients with elevations important in their thyroid hormone levels, in particular free T3, othersymptoms may be present, such as shortness of breath, thermophobia orpalpitation [17].

Graves' disease occurs in about 0.2-0.5% of pregnancies [6, 23]. It is sometimes useful in case of thyrotoxicosis in case of diagnostic doubt to complete the assessment with a TRAb assay [24]. The risk of Graves' disease during pregnancy is linked to the risk of transplacental passage of TRAb and ATS.

Symptoms of thyrotoxicosis may worsen during the 1st trimester under stimulation of CGH and by increased titer of antithyroid antibodies. Secondarily, they decrease due to greater immunotolerance, so the disease improves during pregnancy [6]. If the excess of thyroid hormones in antenatal is not corrected there is a risk of developing congenital central hypothyroidism by negative feedback on fetal TSH. It is important to monitor the TRAb level between the 22nd and 26th week of pregnancy to assess the risk of fetal or neonatal hyperthyroidism.

The other causes of hyperthyroidism in pregnancy are much rarer and are also found in the general population [17]: toxic adenoma, multi-hetero nodular goiter, factitious thyrotoxicosis, subacute or silent thyroiditis, etc.

Uncontrolled, untreated hyperthyroidism that persists during pregnancy, whatever its etiology, can lead to a greater risk of maternal and child complications [25, 26]. We retain a potentially increased risk for the complications listed below.

At the maternal level, we can observe a greater risk [26]: of spontaneous miscarriage (FCS) or fetal death in utero (IUFD), pregnancy-induced hypertension, pre-eclampsia, anemia, infections, thyrotoxic crisis, heart failure, prematurity, postpartum bleeding and caesarean section.

In childhood [27]: intrauterine growth retardation (IUGR), lower birth weight and lower weight for gestational age, congenital malformations, hip dysplasia, neonatal respiratory distress syndrome and neonatal dysthyroidism.

The current general therapeutic approach recommended is not to treat TGH [6, 17].

No prospective study has been carried out to study the occurrence of obstetric complications in women treated with ATS compared to a control group. Very few patients were treated in the retrospective series and no favorable changes were reported. But on a case-by-case basis if the signs of hyperthyroidism are very severe, treatment with ATS can be temporarily instituted over a short period, generally low-dose propylthiouracil (PTU) for a few weeks, most of the time stopped after 22 weeks [15].

The usual management generally consists of a hydro-electrolyte rebalance, and symptomatic treatment for vomiting. Hospitalization may be required depending on the intensity of vomiting. Sometimes recourse to parenteral nutrition or a nasogastric tube may be necessary when vomiting is very severe, uncontrolled in failure of symptomatic treatments, with significant metabolic disorders.

Beta blockers can be used during pregnancy as they control the adrenergic symptoms of thyrotoxicosis, including tachycardia. Their use must be limited in duration. They have not shown teratogenicity but can

induce neonatal bradycardia and hypoglycaemia [7] when used at the end of pregnancy.

If the diagnosis of Graves' disease or toxic adenoma is made, treatment with ATS will be necessary and recommended [5, 19]. Obtaining euthyroidism prevents the obstetric complications that we have seen. All treatments in the ATS class, PTU and CMZ have the same placental distribution [28, 29], and therefore the risk of inducing fetal hypothyroidism. Concerning the use of ATS during pregnancy, cases of fetal malformations have been reported, in particular during the first trimester with the use of CMZ and its derivatives. The malformation rate found is on average 1.6% to 4.1% depending onseries, in children exposed in utero to CMZ [30]. According to some studies, does not observe differences in the incidence of malformation between CMZ and PTU, other found similar incidences [7].

CONCLUSION

Pregnancy hyperthyroidism is a frequently encountered situation. The identification of the cause of hyperthyroidism must be established because it guides the monitoring and management of pregnancy. Hyperthyroidism occurring in the first trimester is most often transient. That of the 2nd and 3rd trimester is most often due to Graves' disease and multihetero-nodular goiter. Recent knowledge of the pathophysiological relationships between thyroid dysfunction and pregnancy, as well as better monitoring of the functionmaternal thyroid during pregnancy in patients with hyperthyroidism, should help prevent maternal-fetal complications of pregnancy-induced thyrotoxicosis. Remember the need for close collaboration between gynecologists, obstetricians and endocrinologists for the management of hyperthyroidism during pregnancy.

REFERENCES

1. Glinoer, D. (1999). What happens to the normal thyroid during pregnancy?. *Thyroid*, *9*(7), 631-635.
2. Glinoer, D. (1997). The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocrine reviews*, *18*(3), 404-433.
3. Kennedy, R. L., Malabu, U. H., Jarrod, G., Nigam, P., Kannan, K., & Rane, A. (2010). Thyroid function and pregnancy: before, during and beyond. *Journal of obstetrics and gynaecology*, *30*(8), 774-783.
4. Männistö, T., Mendola, P., Grewal, J., Xie, Y., Chen, Z., & Laughon, S. K. (2013). Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. *The Journal of Clinical Endocrinology & Metabolism*, *98*(7), 2725-2733.
5. Bober, S. A., McGill, A. C., & Tunbridge, W. M. G. (1986). Thyroid function in hyperemesis gravidarum. *European Journal of Endocrinology*, *111*(3), 404-410.
6. Mestman, J. H. (2012). Hyperthyroidism in pregnancy. *Current Opinion in Endocrinology, Diabetes and Obesity*, *19*(5), 394-401.
7. Cooper, D. S., & Laurberg, P. (2013). Hyperthyroidism in pregnancy. *The lancet Diabetes & endocrinology*, *1*(3), 238-249.
8. Lo, J. C., Rivkees, S. A., Chandra, M., Gonzalez, J. R., Korelitz, J. J., & Kuzniewicz, M. W. (2015). Gestational thyrotoxicosis, antithyroid drug use and neonatal outcomes within an integrated healthcare delivery system. *Thyroid*, *25*(6), 698-705.
9. De Leo, S., Lee, S. Y., & Braverman, L. E. (2016). Hyperthyroidism. *The Lancet*, *2016*.
10. MASIUKIEWICZ, U. S., & BURROW, G. N. (1999). Hyperthyroidism in pregnancy: diagnosis and treatment. *Thyroid*, *9*(7), 647-652.
11. Bournaud, C., & Orgiazzi, J. (2008). Thyroide et grossesse. 2008.
12. Lockwood, C. M., Grenache, D. G., & Gronowski, A. M. (2009). Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations. *Thyroid*, *19*(8), 863-868.
13. Stagnaro-Green, A., Abalovich, M., Alexander, E., Azizi, F., Mestman, J., Negro, R., ... & Wiersinga, W. (2011). Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid*, *21*(10), 1081-1125.
14. Kennedy, R. L., Malabu, U. H., Jarrod, G., Nigam, P., Kannan, K., & Rane, A. (2010). Thyroid function and pregnancy: before, during and beyond. *Journal of obstetrics and gynaecology*, *30*(8), 774-783.
15. Glinoer, D. (2003). Management of hypo-and hyperthyroidism during pregnancy. *Growth hormone & IGF research*, *13*, S45-S54.
16. Goodwin, T. M., Montoro, M., & Mestman, J. H. (1992). Transient hyperthyroidism and hyperemesis gravidarum: clinical aspects. *American journal of obstetrics and gynecology*, *167*(3), 648-652.
17. Goldman, A. M., & Mestman, J. H. (2011). Transient non-autoimmune hyperthyroidism of early pregnancy. *Journal of thyroid research*, *2011*, 142413,
18. Niebyl, J. R. (2010). Nausea and vomiting in pregnancy. *New England Journal of Medicine*, *363*(16), 1544-1550.
19. Alexander, E. K., Pearce, E. N., Brent, G. A., Brown, R. S., Chen, H., Dosiou, C., ... & Sullivan, S. (2017). 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*, *27*(3), 315-389.
20. Goodwin, T. M., Montoro, M. A. R. T. I. N., Mestman, J. H., Pekary, A. E., & Hershman, J. M. (1992). The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. *The Journal of Clinical Endocrinology & Metabolism*, *75*(5), 1333-1337.
21. Chiossi, G., Neri, I., Cavazzuti, M., Basso, G., & Facchinetti, F. (2006). Hyperemesis gravidarum complicated by Wernicke encephalopathy:

background, case report, and review of the literature. *Obstetrical & gynecological survey*, *61*(4), 255-268.

22. Kimura, M., Amino, N., Tamaki, H., Ito, E., Mitsuda, N., Miyai, K., & Tanizawa, O. (1993). Gestational thyrotoxicosis and hyperemesis gravidarum: possible role of hCG with higher stimulating activity. *Clinical endocrinology*, *38*(4), 345-350.
23. Negro, R., & Mestman, J. H. (2011). Thyroid disease in pregnancy. *Best Practice & Research Clinical Endocrinology & Metabolism*, *25*(6), 927-943.
24. Secretariat, W. H. O., Andersson, M., De Benoist, B., Delange, F., & Zupan, J. (2007). Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. *Public health nutrition*, *10*(12A), 1606-1611.
25. Männistö, T., Mendola, P., Grewal, J., Xie, Y., Chen, Z., & Laughon, S. K. (2013). Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. *The Journal of Clinical Endocrinology & Metabolism*, *98*(7), 2725-2733.
26. Su, P. Y., Huang, K., Hao, J. H., Xu, Y. Q., Yan, S. Q., Li, T., ... & Tao, F. B. (2011). Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. *The Journal of Clinical Endocrinology & Metabolism*, *96*(10), 3234-3241.
27. Millar, L. K., Wing, D. A., Leung, A. S., Koonings, P. P., Montoro, M. N., & Mestman, J. H. (1994). Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. *Obstetrics & Gynecology*, *84*(6), 946-949.
28. Mortimer, R. H., Cannell, G. R., Addison, R. S., Johnson, L. P., Roberts, M. S., & Bernus, I. (1997). Methimazole and propylthiouracil equally cross the perfused human term placental lobule. *The Journal of Clinical Endocrinology & Metabolism*, *82*(9), 3099-3102.
29. Momotani, N., Yoshimura Noh, J., Ishikawa, N., & Ito, K. (1997). Effects of propylthiouracil and methimazole on fetal thyroid status in mothers with Graves' hyperthyroidism. *The Journal of Clinical Endocrinology & Metabolism*, *82*(11), 3633-3636.
30. Yoshihara, A., Noh, J., Yamaguchi, T., Ohye, H., Sato, S., Sekiya, K., ... & Ito, K. (2012). Treatment of graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. *The Journal of Clinical Endocrinology & Metabolism*, *97*(7), 2396-2403.