

Controversies in Management of Hyperthyroidism during Pregnancy

Fereidoun Azizi¹, Atieh Amouzegar*¹

Cite this article as: Azizi F, Amouzegar A. Controversies in Management of Hyperthyroidism during Pregnancy. Arch Iran Med. 2017; 20(10): 657 – 568.

The importance of normal thyroid function during pregnancy has compelled the American Thyroid Association to revise its 2011 guidelines¹ to a new set of guidelines in 2016, published in the *Thyroid*.² The new guidelines contain many important recommendations based on some scientific evidence, presented in the last five years and the ATA appointed scientists responsible for this should be congratulated for this commendable piece of work.

Like many other sets of recommendations, however, the 2016 Guidelines of the ATA for “Diagnosis and Management of Thyroid Disease during Pregnancy” suffer from some recommendations that are based mostly on “expert opinion”, and are pointed out as “Weak recommendation, Low quality evidence”. One section that suffers more from weak recommendations is section VIII: Thyrotoxicosis in pregnancy. With all due respect, we would like to express our views on some of these recommendations.

Considerations on side effects of antithyroid drugs (ATD) during pregnancy

Although this subject is controversial in, the ATA 2016 guidelines are centered around one study in the Danish registry.³ This has been a good study focusing on teratogenic effects of ATD, and has shown the association of aplasia cutis, abdominal wall, eyes, urinary, digestive tract, respiratory and VSD anomalies in fetuses of mothers who used methimazole (MMI) and also face and neck and urinary anomalies with PTU. However, reviewing related recent papers shows that another article has documented an association only for aplasia cutis and abdominal wall anomaly with MMI and none with PTU use during pregnancy.⁴ In addition, four other papers failed to report such associations with ATD use in pregnancy and birth defects.⁵⁻⁸ Although papers with negative findings may have had lower numbers of exposed mothers and questions in their design, at least one, reported by Korelitz *et al.* in 2013, had examined 108 and 915 mothers exposed to MMI and PTU, respectively with 634,858 controls, and found no rise in defects detected with ATD.⁶ While emphasizing the possible teratogenic side effects of ATD during pregnancy, a balanced evidence-based discussion and recommendations could better explain the existing controversies.

Authors' affiliations: ¹Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

***Corresponding author and reprints:** Atieh Amouzegar MD, P.O. Box: 1985717413, Tehran, Iran. Tel: +98-21- 22409309, Fax: +98-21- 22402463, E-mail: amouzegar@endocrine.ac.ir.

Accepted for publication: 20 September 2017

Considerations on withdrawing ATD in early pregnancy

While there is no data related to the benefits of ATD withdrawal in early pregnancy, the 2016 guidelines recommended that if a newly-pregnant woman with Graves' disease is euthyroid on a low dose of ATD, the physician should consider discontinuing all ATD medications, given the potential teratogenic effects.² It is clear that 30–50% of GD patients with low or undetectable TSH receptor antibody (TRAb) titers at the end of treatment may experience relapse of hyperthyroidism following ATD withdrawal.⁹ The relapse of hyperthyroidism occurs in 20% within the first 6 months after ATD withdrawal.¹⁰ Although it has been shown that only 5% of TRAb negative patients become hyperthyroid within 8 weeks after ATD withdrawal,¹¹ it is not known what portion of GD patients entering pregnancy are TRAb negative and how many of the so-called “low clinical risk” patients will experience the relapse of hyperthyroidism, which may be abrupt, severe and difficult to control during pregnancy, and may threaten both mother and fetus with severe complications.¹²

The risk of rapid relapse of hyperthyroidism after ATD withdrawal has not been determined, and the guideline states that no specific single parameter may be used to assign this risk. This is very true; however, it is expected that guidelines provide more objective and specific criteria for selection of patients before ATD withdrawal.

In addition, it is known that some severe, although rare, complications of ATD including liver failure may develop within the first months after re-initiation of therapy¹³ and may complicate the management of thyrotoxicosis during pregnancy.

It has been stated that the crucial teratogenic period is between gestation weeks 6 and 10.¹⁴ In non-pregnant subjects, the occurrence of hyperthyroidism within 5 weeks after ATD withdrawal is very rare; therefore, if a physician wants to discontinue ATD in this critical period, it may be advised to re-initiate ATD treatment after the 10th week of gestation, even if the woman is euthyroid, to avoid relapse of hyperthyroidism during the rest of pregnancy.

Management of a woman with GD during pregnancy counseling and after conception is complex, delicate and needs further evidence-based data. On the other hand, changing guidelines and recommendations without strong evidence adds to these complexities and makes management of patients very difficult, in particular during crucial periods of gestation. Should scientists be advised to change recommendations only if they have hard data, and avoid revising “expert opinions” by “expert opinions”?

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