Original Article

THYROID DISEASE IN PREGNANCY

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Objective: Aim of the review is to determine the effect of thyroid dysfunction on the course of pregnancy.

Material and Methods: Medline, Embase (from 2000 to 2011) and research articles. There was no language restriction for any of these searches. Studies included were randomized clinical trials, cohort and case control studies.

Results: There are few prospective population based cohort studies which study the effect of thyroid dysfunction on fetal development. There was a prospective population based cohort study in china. 1017 women with singleton pregnancy participated in this study. The study showed that clinical hypothyroidism was associated with increased fetal loss, low birth weight, and congenital malformations. The sub clinical hypothyroidism was associated with increased fetal distress, preterm delivery, poor vision development, and neurodevelopment delay. The clinical hyperthyroidism was associated with hearing dysplasia. A systemic review and meta-analysis found a strong association between clinical hypothyroidism and preeclampsia, perinatal mortality and lower IQ in the child. They also found an association between thyroid autoimmunity and unexplained subfertlity, miscarriages, recurrent miscarriages and preterm birth.

Conclusion: The management of thyroid disease in pregnancy is important as thyroid function undergo changes which can adversely affect pregnancy and the fetus.

Keywords: pregnancy, thyroid, fetus.

Introduction

Thyroid disorders are common endocrine problems in pregnancy. The incidence of thyroid disease is common in reproductive age therefore it need to be recognized and treated. The thyroid in pregnancy undergo metabolic, immunological and haematological changes. Thyroid dysfunction if not treated has adverse affect on both the mother and the fetus.

Search Strategy

MEDLINE, EMBASE (from 2000 to 2011) and research articles. There was no language restriction for any of these searches. Studies included were randomized clinical trials, cohort and case control studies.

Results

There are few prospective population based cohort studies which study the effect of thyroid dysfunction on fetal development. There was a prospective population based cohort study in china. 1017 women with singleton pregnancy participated in this study. The study showed that clinical hypothyroidism was associated with increased fetal loss, low birth weight, and congenital malformations. The sub clinical hypothyroidism was associated with increased fetal distress, preterm delivery, poor vision development, and neurodevelopment delay .The clinical hyperthyroidism was associated with hearing dysplasia.[1] A systemic review and meta-analysis found a strong association between clinical hypothyroidism and preeclampsia, perinatal mortality and lower IQ in the child. They also found an association between thyroid autoimmunity and unexplained subfertlity, miscarriages, recurrent miscarriages and preterm birth.[2] Another study showed that thyroid dysfunction may predispose to late pre eclampsia. In 102 singleton pregnancies that developed late pre eclampsia had mean arterial pressure (MAP), uterine artery pulsatility index (PI) maternal serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) measured at 11 to 13 weeks of gestation. These values were compared with values of normal 4318 pregnancies.[3] This study showed that maternal TSH can be helpful in prediction of late pre eclampsia , in combination with maternal history, measurement of MAP and uterine artery PI.

In a population based cohort study in Netherlands, 3659 children with their mothers were included. The result showed that an increase in FT 4 predicated a

Low risk of expressive language delay at 30 months. However low thyroxine level was associated with higher risk of expressive language delay at all ages.[4]

In a prospective cohort study in 8 women in early pregnancy with sub clinical hypothyroidism and 8 women with euthyroid serum sampling of thyrotropin thyroglobuln, thyroxine, triiodothronine, free thyroxine, free triiodothronine oestradiol, progesterone , human chorionic gonadotropin and prolactin were done weekly from 5 to 12 weeks of gestation . Women with sub clinical hypothyroidism were treated with thyroxine (50 microgram daily) until 12 weeks of gestation. The thyroid function in sub clinical hypothyroidism followed similar changes to euthyroid

Therefore it was less likely to cause higher miscarriage rate as observed in sub clinical hypothyroidism.[5]

A retrospective study of 5 years in women undergoing artificial reproduction showed that in euthyroid women the pregnancy and delivery rates were not affected by presence of antibodies. . However those women with antibodies positive who failed to become pregnant or miscarried showed higher level of TSH.[6]

In a prospective follow up study of 1058 Dutch Caucasian of healthy pregnant women during the three trimesters, were followed up from 12 weeks of gestation to term. The study showed women who had breech presentation had higher level of TSH as compared to those with cephalic presentation at 36 weeks .[7]In another prospective cohort in 141 women with singleton breech > =35 weeks concluded higher TSH level increases the risk of failure of external cephalic version.[8]

Iodine is essential for normal fetal development and its deficiency is common in Western Europe .In a study of 110 women in northern part of Paris revealed iodine deficiency did not correlate significantly with maternal thyroid parameters but affected the fetal thyroid gland. [9] In a study of 114 French pregnant women who had insufficient iodine intake had hypothroxinemia in the third trimester.[10]

Iodine status was assessed in 330 pregnant women in Nice in the third trimester. This study showed that this population had iodine deficiency.[11] In another study, iodine status was studied in pregnant women residing in effective iodization salt programme area. The study concluded that though iodine was adequate in this population but iodine deficiency still existed in some.[12]A cross sectional voluntary screening in a maternity unit of teaching hospital in Turkey involving 70 mothers with their full term neonates found iodine deficiency inspite of salt iodization programme.[13] Similarly Aran Valley in Spain has a longstanding history of iodine deficiency affecting the pregnant women as well .[14].Another study was conducted in Isfahan in Iran after 8 years of iodized salt. No iodine deficiency was seen in Isfahani pregnant women. Thyroid size also did not increase in pregnancy.[15] In a cross sectional observational study of 150 pregnant women in Toronto, Ontario and Canada found lower rate of iodine deficiency compared to previously reported which may be due to universal salt iodization in Canada.[16]

There have been many studies regarding the assessment of thyroid function in pregnancy. In Australia serum sample was collected from 2159 pregnant women at 9-13 weeks of gestation. The result showed that reference interval of TSH in the first trimester of pregnancy differed from non pregnant women. They found out that they were missing 20.5 % of cases by using the general laboratory range for the pregnant women.[17] Similarly another study showed that reference interval in second trimester was different from nonpregnant level.[18] Another study in Japan on 522 pregnant and puerperal women concluded maternal thyroid function especially TSH and free T4 changed during pregnancy .[19] Fetal thyroid gland monitoring done by skilled ultrasonographer can be a good diagnostic tool has been concluded in different studies.[20-22]

Discussion

The management of thyroid disease in pregnancy is important as thyroid function undergo changes which can adversely affect pregnancy and the fetus. In pregnancy thyroid hormone demand is increased which may worsen the thyroid disorder which was unnoticed before. Few weeks after conception serum thyroid binding globulin increases to 2 to 3 fold. This lead to increase in thyroid hormone 1.5 times greater then pre-pregnancy. In woman with pre existing thyroid dysfunction, thyroid function should be normalized prior to conception. In the early pregnancy, fetal thyroxine is taken from the mother, the fetal thyroid starts functioning in the second trimester but the reserves of the fetal gland are low, thus maternal thyroid hormones contribute to total fetal thyroid hormone concentrations until birth.

Thyroid stimulating hormone (TSH) produced by the pituitary gland is responsible for regulating the release of thyroid hormone in the body. If there is a thyroid dysfunction it may result in less or excess production

0.45 and 4.5 mIU/l is considered normal and indicates euthyroidism .However the normal TSH level in pregnancy is lower and 2.5 mIU/l is considered as the upper range cut off[23] .Studies have shown that the risk for miscarriage and preterm delivery were increased when the level was higher .The presence of thyroid antibodies may further complicate this situation. Women with positive antibodies are at a 2-fold increased risk for miscarriage .Studies have shown antithyroid antibodies are prevalent in the first two trimesters of pregnancy.[24]

Iodine is in the important components of two hormones of T4 and T3 produced by the thyroid glands necessary for normal growth and development. The serum T4 and T3 decrease in the second and third trimester. This decrease is further noticeable when iodine in maternal diet is deficient. The iodine deficiency in fetus causes mental retardation in the child.[25] If iodine supplementation is provided on time mental retardation can be prevented.[26,27] In order for pregnant women to produce enough thyroid hormones to meet her as well as the fetus requirements, a 50% increase in iodine intake is recommended. There is clear evidence that severe iodine deficiency in pregnancy impairs brain development in the child. However, only two intervention trials have assessed neurodevelopment in children of moderately iodine deficient mothers and concluded neurodevelopment improved in children of mothers supplemented with iodine earlier rather than late in pregnancy; both studies were not randomised and were uncontrolled.[26] Iodine deficiency is still a problem in many areas. Therefore these areas should be monitored and supplements provided accordingly.

The early recognization of thyroid disease in pregnancy and appropriate treatment would improve the maternal and fetal outcome. The care of pregnant woman with thyroid dysfunction requires coordination with several healthcare professionals. Hypothyroidism is common in pregnancy compared to hyperthyroidism. The presentation of hypothyroidism may be difficult to differentiate from symptoms of pregnancy. Multiple studies has confirmed the risks of complications such as miscarriages, pre eclampsia, anaemia abruption and postpartum haemorrhage in pregnant women with thyroid disease.[26,28] The fetus may have preterm delivery low birth weight and neonatal respiratory distress.[29] A three-fold risk of placental abruption and a two-fold risk of pre-term delivery were reported in mothers with sub clinical hypothyroidism.[30] Both types of thyroid dysfunction may lead to detrimental complications in mother and child and therefore timely recognition and treatment is essential.

There are many areas of agreement and controversies in literature. The agreements are such as on the reference range of thyroid function in pregnant women and proper interpretation of abnormalities .Those on thyroxine requiring increase in the dose in pregnancy .The drug given in the first trimester with Graves hyperthyroidism is only Propylthiouracil and then carbimazole. Iodine supplementation in case of iodine deficiency for proper neurodevelopment. The areas of controversy are screening of thyroid function in early pregnancy in all the pregnant women and what tests are appropriate. There are no adequate studies to support universal screening in pregnant women. Universal screening in all pregnant women can only be justified when there is evidence of beneficial outcomes from randomised controlled trials.

Conclusion

The management of thyroid disease in pregnancy is important as thyroid function undergo changes which can adversely affect pregnancy and the fetus.

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References

1. Pu-Yu Su, Kun Huang, Jia-Hu Hao, Ye-Qin Xu, Shuang-Qin Yan, Tao Li, Yuan-Hong Xu and Fang-Biao Tao Maternal Thyroid Function in the First Twenty Weeks of Pregnancy and Subsequent Fetal and Infant Development: A Prospective Population-Based Cohort Study in China Journal of Clinical Endocrinology & Metabolism, October 2011, vol. /is. 96/10(3234-41),0021-972X; 1945-7197
2. Van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, Bisschop PH. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod Update. 2011 Sep-Oct;17(5):605-19. Epub 2011 May 28.
3. Ghalia Ashoor, Nerea Maiz, Micheal Rotas, Nikos A. Kametas and Kypros H. Nicolaides Maternal

Weeks of Gestation in Women with Hypothyroidism Treated by Thyroxine Prenatal Diagnosis, November 2010, vol. /is. 30/11(1032-8), 0197-3851; 1097-0223

4. Jens Henrichs,Jacoba J. Bongers-Schokking,Jacqueline J. Schenk,Akhgar Ghassabian,Henk G. Schmidt,Theo J. Visser,Herbert Hooijkaas,Sabine M. P. F. de Muinck Keizer-Schrama,Albert Hofman,Vincent V. W. Jaddoe,Willy Visser,Eric A. P. Steegers,Frank C. Verhulst,Yolanda B. de Rijke andHenning Tiemeier Maternal Thyroid Function during Early Pregnancy and Cognitive Functioning in Early Childhood: The Generation R Study . Journal of Clinical Endocrinology & Metabolism, September 2010, vol. /is.95/9(4227-34), 0021-972X; 1945-7197.
5. Christian De Geyter, Sabine Steimann, Beat Müller, Marius E. Kränzlin, Christian Meier Pattern of Thyroid Function During Early Pregnancy in Women Diagnosed with Subclinical Hypothyroidism and Treated with l-Thyroxine is Similar to That in Euthyroid Controls. Thyroid, January 2009, vol. /is. 19/1(53-9), 1050-7256; 1557-9077.
6. R. Negro1, G. Formoso1, L. Coppola2, G. Presicce2, T. Mangieri2, A. Pezzarossa3, and D. Dazzi3 Euthyroid women with autoimmune disease undergoing assisted reproduction technologies: The role of autoimmunity and thyroid function.Journal of Endocrinological Investigation, January 2007, vol. /is. 30/1(3-8), 0391-4097; 1720-8386
7. S. M. I. Kuppens, L. Kooistra, H. A. Wijnen, S. Crawford, H. L. Vader, T. H. M. Hasaart, S. G. Oei and V. J. Pop High thyrotrophin levels at end term increase the risk of breech presentation. Clinical Endocrinology, June 2010, vol. /is. 72/6(820-4), 0300-0664; 1365-2265.
8. Simone M Kuppens, Libbe Kooistra, Tom H Hasaart, Riet W van der Donk, Huib L Vader, Guid S Oei and Victor J Pop . Maternal thyroid function and the outcome of external cephalic version: a prospective cohort study BMC pregnancy and childbirth, 2011, vol. /is. 11/ (10), 1471-2393 (2011). Dominique Luton, Corinne Alberti, Edith Vuillard, Guillaume Ducarme, Jean François Oury, Jean Guibourdenche Iodine Deficiency in Northern Paris Area: Impact on Fetal Thyroid Mensuration PLoS ONE [Electronic Resource], 2011, vol. /is. 6/2(e14707), 1932-6203; 1932-6203
10. N. Bourcigaux, C. Lepoutre-Lussey, J. Guéchot, B. Donadille, I. Faugeron, S. Ouzounian, S. Christin-Maître, P. Bouchard, F. Duron Thyroid function at the third trimester of pregnancy in a Northern French population. Annales d Endocrinologie, December 2010, vol. /is. 71/6(519-24), 0003-4266; 0003-4266.
11. S. Hiéronimus, M. Bec-Roche, P. Ferrari, N. Chevalier, P. Fénichel, F. Brucker-Davis Iodine status and thyroid function of 330 pregnant women from Nice area assessed during the second part of pregnancy . Annales d Endocrinologie, September 2009, vol. /is. 70/4(218-24), 0003-4266;0003-4266.
12. Yanling Wang, Zhongliang Zhang, Pengfei Ge, Yibo Wang, Shigong WangIodine status and thyroid function of pregnant, lactating women and infants (0-1 yr) residing in areas with an effective Universal Salt Iodization program Asia Pacific Journal of Clinical Nutrition, 2009, vol. /is. 18/1(34-40),0964-7058; 0964-7058
13. Selim Kurtoglu, Mustafa Akcakus, Celebi Kocaoglu, Tamer Gunes and Nurten Budak, et al. Iodine status remains critical in mother and infant in Central Anatolia (Kayseri) of Turkey.European Journal of Nutrition, October 2004, vol. /is. 43/5(297-303), 1436-6207; 1436-6207.
14. L. Vila, G. Legaz, C. Barrionuevo, M.L. Espinel, R. Casamitjana, J. Muñoz, M. Serra-Prat, and M. Puig-Domingo Iodine status and thyroid volume changes during pregnancy: results of a survey in Aran Valley (Catalan Pyrenees). Journal of Endocrinological Investigation, October 2008, vol. /is. 31/10(851-5),0391-4097; 1720-8386.
15. Rezvanian H, Aminorroaya A, Majlesi M, Amini A, Hekmatnia A, Kachoie A, Amini M, Emami JThyroid size and iodine intake in iodine-repleted pregnant women in Isfahan, Iran. Endocr Pract. 2002 Jan-Feb;8(1):23-8
16. Haddow JE The new American Thyroid Association Guidelines for thyroid disease during pregnancy and postpartum: a blueprint for improving prenatal care Thyroid, October 2011, vol. /is. 21/ (A10), 1050-7256
17. Rhonda M Gilbert, Narelle C Hadlow, John P Walsh, Stephen J Fletcher, Suzanne J Brown, Bronwyn G Stuckey and Ee Mun Lim Assessment of thyroid function during pregnancy: first-trimester (weeks 913) reference intervals derived from Western Australian women Medical Journal of Australia, September 2008, vol. /is. 189/5(250-3), 0025-729X; 0025-729X.
18. Sonia L. La'ulu and William L. Roberts Second-trimester reference intervals for thyroid tests: the role of ethnicity Clinical Chemistry, September 2007, vol. is. 53/9(1658-64), 0009-9147; 0009-9147
19. Hiroko KURIOKA, Kentaro TAKAHASHI, Kohji MIYAZAKI Maternal thyroid function during pregnancy and puerperal period Endocrine Journal, October 2005, vol. /is. 52/5(587-91), 0918-8959; 0918-8959
20. Dominique Luton, Isabelle Le Gac, Edith Vuillard, Mireille Castanet, Jean Guibourdenche, Michèle Noel, Marie-Elisabeth Toubert, Juliane Léger, Christi

Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. Journal of Clinical Endocrinology & Metabolism, November 2005, vol. /is. 90/11(6093-8), 0021-972X; 0021-972X

21. Pierre-François Ceccaldia, Sandra Cohenb, Edith Vuillarda, Fabien Guimiotc, Anne-Lise Delezoidec, Olivier Poujadea, Guillaume Ducarmea, Jean-François Ourya, Dominique Lutona Correlation between Colored Doppler Echography of Fetal Thyroid Goiters and Histologic Study Fetal Diagn Therapy 2010;27:233-235 (DOI: 10.1159/000304269
22. P Zamperini, B Gibelli, D Gilardi, N Tradati, F Chiesa Pregnancy and thyroid cancer: ultrasound study of foetal thyroid. Acta Otorhinolaryngologica Italica, 2009, vol. /is. 29/6(339-344), 0392-100X; 1827-675X
23. Lazarov I, Cocovska N Autoimmune thyroid disease and pregnancy--challenge or routine Akush Ginekol (Sofiia). 2011; 50(2):39-41. (In Bulgarian)
24. Mintziori G., Anagnostis P., Toulis K. A., Goulis DG Thyroid diseases and female reproduction Minerva Med. 2012 Feb; 103(1):47-62.
25. Azad Reza Mansourian A review on the metabolic disorders of iodine deficiency. Pak J Biol Sci. 2011 Apr 1; 14(7):412-24
26. Sheila A. Skeaff Skeaff Iodine deficiency in pregnancy: the effect on neurodevelopment in the child Nutrients. 2011 Feb; 3(2):265-73. Epub 2011 Feb 18.
27. Gabriella Morreale de Escobar, María Jesús Obregón and Francisco Escobar del Rey Iodine deficiency and brain development in the first half of pregnancy Public Health Nutr. 2007 Dec; 10(12A):1554-70
28. Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG. Subclinical thyroid disease and the incidence of hypertension in pregnancy Gärtner R Obstet Gynecol. 2012 Feb; 119(2 Pt 1):315-20.
29. Idris I, Srinivasan R, Simm A, Page RC Maternal hypothyroidism in early and late gestation: effects on neonatal and obstetric outcome Clin Endocrinol (Oxf). 2005 Nov;63(5):560-5.
30. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG Subclinical hypothyroidism and pregnancy outcomes Obstet Gynecol. 2005;