

Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence

Shakila Thangaratinam, senior lecturer/consultant in obstetrics and gynaecology and clinical epidemiology,¹ Alex Tan, academic foundation trainee,² Ellen Knox, consultant obstetrician/subspecialist in fetal medicine,³ Mark D Kilby, professor of fetal medicine,^{2,3} Jayne Franklyn, professor of medicine,² Arri Coomarasamy, reader/consultant gynaecologist/subspecialist in reproductive medicine and surgery²

¹Centre for Health Sciences, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AD, UK

²School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT

³Fetal Medicine Centre, Birmingham Women's Foundation Trust, Edgbaston, Birmingham B15 2TG

Correspondence to: A Coomarasamy
a.coomarasamy@bham.ac.uk

Cite this as: *BMJ* 2011;342:d2616
doi:10.1136/bmj.d2616

ABSTRACT

Objectives To evaluate the association between thyroid autoantibodies and miscarriage and preterm birth in women with normal thyroid function. To assess the effect of treatment with levothyroxine on pregnancy outcomes in this group of women.

Design Systematic review and meta-analysis.

Data sources Medline, Embase, Cochrane Library, and SCISEARCH (inception-2011) without any language restrictions. We used a combination of key words to generate two subsets of citations, one indexing thyroid autoantibodies and the other indexing the outcomes of miscarriage and preterm birth.

Study selection Studies that evaluated the association between thyroid autoantibodies and pregnancy outcomes were selected in a two stage process. Two reviewers selected studies that met the predefined and explicit criteria regarding population, tests, and outcomes.

Data synthesis Odds ratios from individual studies were pooled separately for cohort and case-control studies with the random effects model.

Results 30 articles with 31 studies (19 cohort and 12 case-control) involving 12 126 women assessed the association between thyroid autoantibodies and miscarriage. Five studies with 12 566 women evaluated the association with preterm birth. Of the 31 studies evaluating miscarriage, 28 showed a positive association between thyroid autoantibodies and miscarriage. Meta-analysis of the cohort studies showed more than tripling in the odds of miscarriage with the presence of thyroid autoantibodies (odds ratio 3.90, 95% confidence interval 2.48 to 6.12; $P<0.001$). For case-control studies the odds ratio for miscarriage was 1.80, 1.25 to 2.60; $P=0.002$). There was a significant doubling in the odds of preterm birth with the presence of thyroid autoantibodies (2.07, 1.17 to 3.68; $P=0.01$). Two randomised studies evaluated the effect of treatment with levothyroxine on miscarriage. Both showed a fall in miscarriage rates, and meta-analysis showed a significant 52% relative risk reduction in miscarriages with levothyroxine (relative risk 0.48, 0.25 to 0.92; $P=0.03$). One study reported on the effect of

levothyroxine on the rate of preterm birth, and noted a 69% relative risk reduction (0.31, 0.11 to 0.90).

Conclusion The presence of maternal thyroid autoantibodies is strongly associated with miscarriage and preterm delivery. There is evidence that treatment with levothyroxine can attenuate the risks.

INTRODUCTION

Miscarriage, the loss of a pregnancy before 24 weeks of gestation, affects up to one in five women who conceive, making it the commonest complication of pregnancy.¹ Preterm birth, delivery of a baby between 24 and 37 completed weeks of gestation, occurs in 6-10% of pregnancies.² Up to 85% of neonatal deaths are attributable to preterm birth (especially those delivered before 28 weeks). Of those who survive, around 10% have long term disability.³ The cost of preterm birth is £93m a year in the United Kingdom.³ This includes healthcare costs (including neonatal care), education, and costs to the parents.

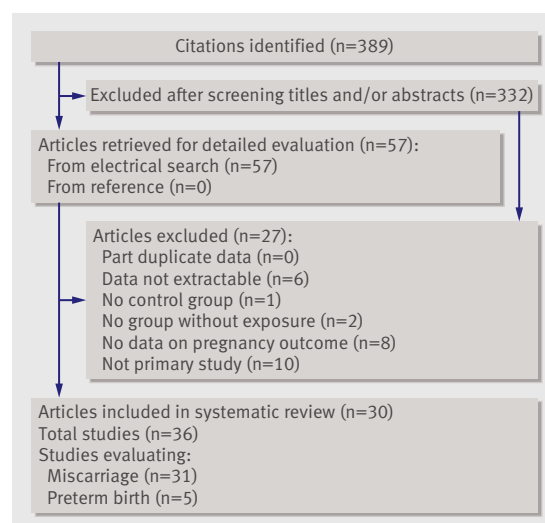


Fig 1 Flow chart of study selection in review of association between thyroid autoantibodies and adverse pregnancy outcome

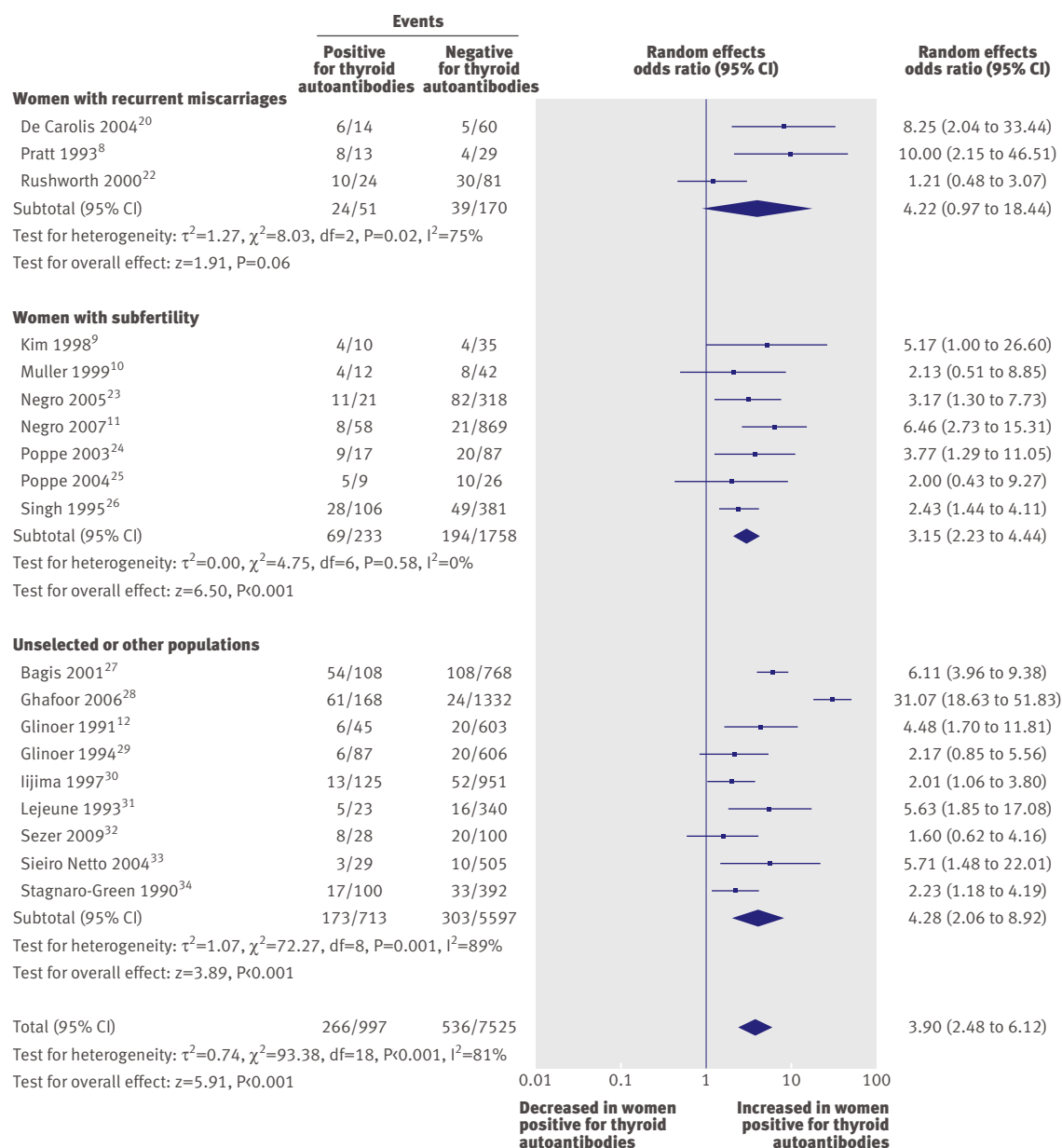


Fig 2 | Association between thyroid autoantibodies and miscarriage in cohort studies

There is evidence that thyroid autoimmunity is an important risk factor for miscarriage and preterm birth.⁴ The presence of thyroid autoantibodies is relatively common in women of reproductive age. In an “unselected” population of women, the prevalence ranges from 6% to 20%,^{4,5} being even higher in women with a history of recurrent pregnancy loss, at around 17–33%,^{6–8} and in women with a history of subfertility, at around 10–31%.^{9–11} In the developed world, thyroid autoimmunity is the main cause of hypothyroidism, which itself results in poor obstetric outcomes. Even in women with biochemically normal thyroid function, studies have reported an association between the presence of thyroid autoantibodies, particularly thyroid peroxidase antibodies and adverse pregnancy outcomes, including miscarriage, preterm birth, and adverse neurodevelopmental sequelae in children.^{12,13} The exact mechanisms

of these associations are unknown, though two have been proposed. Firstly, the presence of thyroid autoantibodies in women with normal thyroid function could be associated with a subtle deficiency in the availability of thyroid hormones (a fall in circulating free thyroid hormones within the reference range) or a lower capacity of the thyroid gland to adequately rise to the demand for augmented synthesis of thyroid hormones required in pregnancy.¹⁴ Given that minor perturbations in thyroxine concentrations within the normal range can lead to an association between thyroid autoantibodies and adverse pregnancy outcomes, trials have been conducted to evaluate the effects of supplementation with levothyroxine on pregnancy outcomes in women with normal thyroid function who tested positive for thyroid autoantibodies. Secondly, thyroid autoantibodies might be an indicator of an underlying

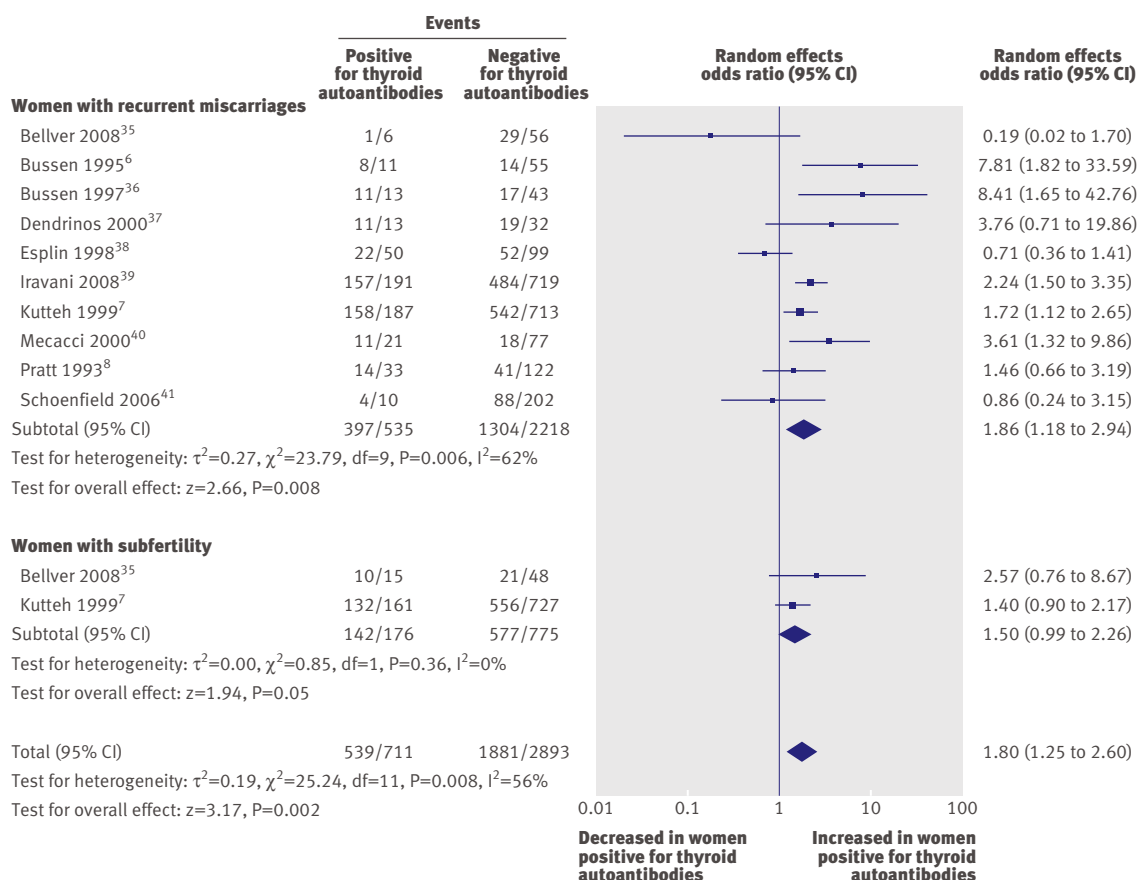


Fig 3 | Association between thyroid autoantibodies and miscarriage in case-control studies

enhanced global autoimmune state. This itself can have a direct adverse effect on placental or fetal development.¹⁴

Given the importance of the potential association between thyroid autoantibodies and adverse pregnancy outcomes, we systematically reviewed and meta-analysed the association between thyroid autoantibodies and miscarriage and preterm birth. Given the possible role of levothyroxine in improving pregnancy outcomes, we also reviewed the available randomised evidence on the effect of treatment with levothyroxine on pregnancy outcomes.

METHODS

This systematic review was conducted with a prospective protocol with widely recommended methods.¹⁵

Identification of studies

We searched Medline (1951-2011), Embase (1974-2011), the Cochrane Library (2011), and SCISEARCH (1974-2011) for relevant citations and examined the reference lists of all known primary and review articles to identify cited articles not captured by the electronic searches. Language restrictions were not applied. We used a combination of MeSH and text words to generate two subsets of citations, one indexing thyroid autoantibodies (“thyroid autoimmune antibodies”, exp thyroid/ AND exp antibodies, thyroid AND autoimmune AND antibodies) and the other indexing

outcomes (“miscarriage”, “abortion”, “pregnancy loss”, “preterm”, “premature”, “early labo(u)r”, “pret \$”). These subsets were combined with “AND” to generate a subset of citations relevant to our research question.

Study selection and data extraction procedures

The electronic searches were scrutinised and two independent reviewers (ST and EK) obtained full manuscripts of all citations that were likely to meet the predefined selection criteria. Studies were selected if they included women with normal thyroid function who tested positive for thyroid autoantibodies, and the outcomes included adverse maternal and fetal outcomes. We excluded articles in which women were known to have overt biochemical hypothyroidism or hyperthyroidism. When disagreements occurred, they were resolved by consensus and discussion with a third reviewer (AC). In cases of duplicate publication, we selected the most recent and complete versions.

Information was extracted from each selected article on study characteristics, quality, and test results. Data were used to construct 2×2 tables of thyroid autoantibody results (test positive if concentrations were above a threshold as defined in the primary study, and test negative if these were below the threshold) and pregnancy outcomes (miscarriage and preterm delivery). We also extracted data on mean age and serum

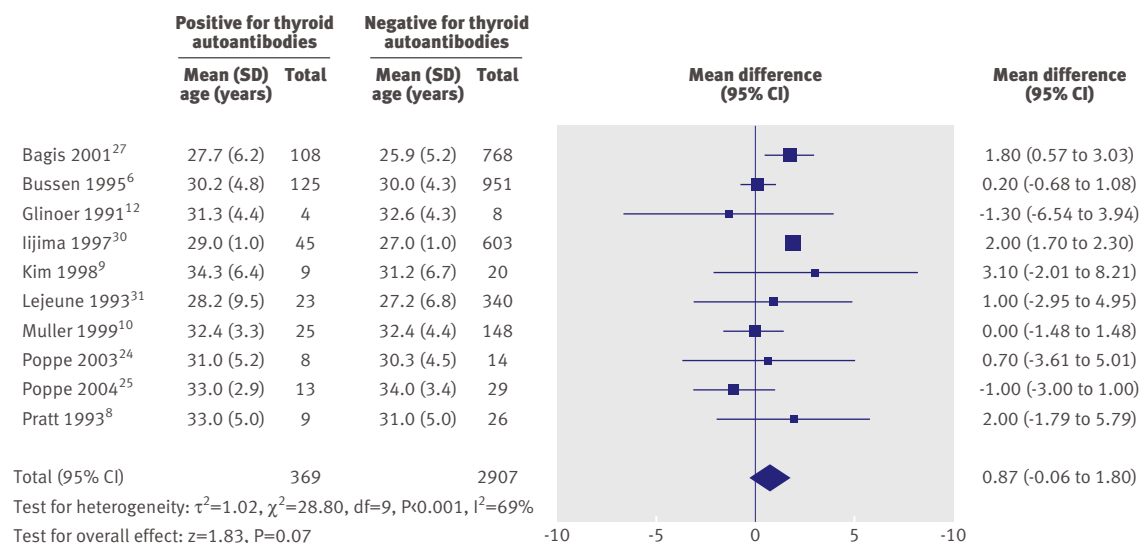


Fig 4 | Comparison of age between women positive and negative for thyroid autoantibodies in included studies

concentrations of thyroid stimulating hormone and free thyroxine. For the randomised trials, we extracted data on study population, quality of the methods, details of the interventions, and outcomes.

Assessment of quality of methods

We used the Newcastle-Ottawa scale¹⁶ to assess methodological quality of the selected studies, with the components of study design that are related to internal validity. Information on adequacy of definition of cases or cohorts, representativeness of the sample, selection and evaluation of controls, comparability, ascertainment of exposure, and outcome were evaluated for cohort and case-control studies.¹⁶ The study was considered to have low risk of bias if it scored a maximum of 4 for selection, 2 for comparability, and 3 for assessment of outcome or ascertainment of exposure. Any study that scored 1 or zero for selection or zero for comparability or for outcome assessment was categorised as having a high risk of bias. Studies that scored in between were rated as having medium risk of bias.

We assessed quality of randomised trials evaluating the effectiveness of levothyroxine according to appropriate randomisation, concealment of allocation, blinding, analysis by intention to treat, and follow-up rates. A quality score for the randomised trials was given on Jadad's scale.¹⁷

Data synthesis

Odds ratios from individual studies were pooled separately for the cohort and case-control studies with the random effects model. Heterogeneity of treatment effects was evaluated graphically with forest plots and statistically with χ^2 and I^2 tests. We generated the pooled mean difference in age and weighted mean difference in serum thyroid stimulating hormone between groups with positive and negative results for thyroid autoantibodies. All analyses were performed with Stata 10.0 and Revman 5 statistical software.^{18,19}

RESULTS

Figure 1 summarises the processes of literature identification and selection of studies evaluating the relation between thyroid autoantibodies and adverse pregnancy outcomes. From the 389 citations identified from electronic and hand searches, we included 30 primary articles with 36 studies (31 for miscarriage and five for preterm birth) in the systematic review.

Thyroid autoantibodies and miscarriage

Thirty one studies (12 126 women)^{6-12,20-41} evaluated the association between thyroid autoantibodies and miscarriage. Nineteen studies were cohort studies, and 12 were case-control studies. Thirteen studies (three cohort, 10 case-control) evaluated the association in women with recurrent miscarriage, nine studies (seven cohort, two case-control) in women with subfertility and nine cohort studies in unselected or other populations. The studies were judged to have low risk of bias for assessment of outcome (19/19 cohort studies) and ascertainment of exposure (12/12 case-control studies) on the Newcastle-Ottawa scale.¹⁶ Nearly half the cohort studies (9/19) had low selection bias and the others (10/19) had medium selection bias. All the case-control studies had medium selection bias. Eight of the 19 (42%) cohort studies had established good comparability of the groups compared with 16% (2/12) of the case-control studies.

Appendix 1 on bmj.com provides details of the characteristics of the women in the included studies. All studies tested for thyroid peroxidase antibodies. Studies varied in the frequency and timing of the autoantibody testing, ranging from testing before pregnancy, in early pregnancy, and after delivery or miscarriage. The commonest threshold concentration of thyroid peroxidase for a diagnosis of positive thyroid autoantibodies was >100 U/ml. The various thresholds used to define positivity for thyroid autoantibodies are in appendix 1 on bmj.com.

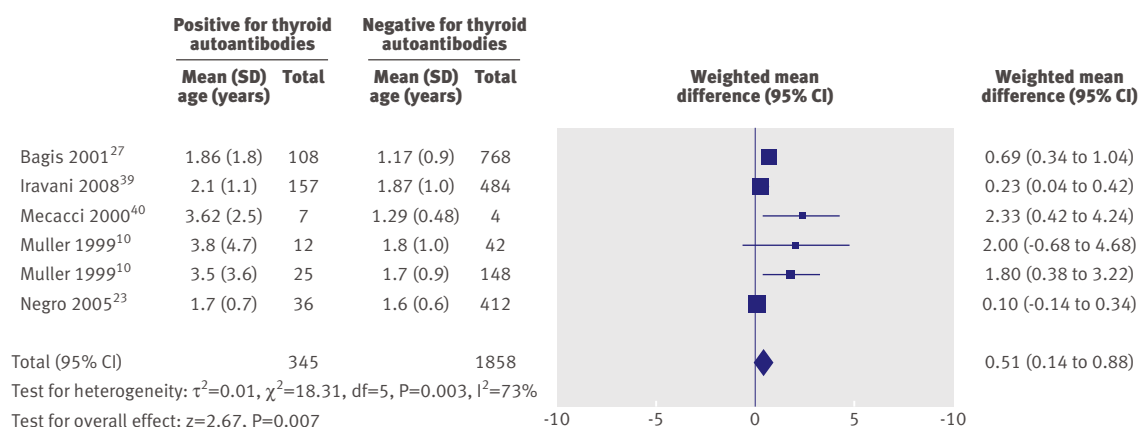


Fig 5 | Comparison of serum thyroid stimulating hormone (TSH) concentration between women positive and negative for thyroid autoantibodies in included studies

Twenty eight of the 31 (19/19 cohort and 9/12 case-control) studies showed a positive association between thyroid autoantibodies and spontaneous miscarriage. Meta-analysis of the cohort studies found more than tripling in the odds of miscarriage in the presence of thyroid autoantibodies (odds ratio 3.90, 95% confidence interval 2.48 to 6.12; $P<0.001$) (fig 2). The odds of miscarriage with thyroid autoantibodies was increased for women with recurrent miscarriages (4.22, 0.97 to 18.44; $P=0.06$), women with subfertility (3.15, 2.23 to 4.44; $P<0.001$), and unselected or other populations (4.28, 2.06 to 8.92; $P<0.001$). There was significant unexplained heterogeneity for studies in women with recurrent miscarriage ($I^2=75\%$) and the unselected population ($I^2=89\%$). There was no evidence of heterogeneity for studies in women with subfertility ($I^2=0\%$) (fig 2).

Meta-analysis of the 12 case-control studies also showed an increase in the odds of miscarriage in women with normal thyroid function and thyroid autoantibodies (1.80, 1.25 to 2.60; $P=0.002$) (fig 3). The odds of miscarriage was increased in two subgroups: women with recurrent miscarriage (1.86, 1.18 to 2.94; $P=0.008$) and women with subfertility (1.50, 0.99 to 2.26; $P=0.05$).

As increasing maternal age is an “independent” risk factor for miscarriage,⁴² we examined the difference in the mean age of women who were positive or negative for thyroid autoantibodies through a meta-analysis of the 10 studies that reported age. There was no significant difference between the groups (weighted mean difference 0.87 years, -0.06 to 1.80 years; $P=0.07$, fig 4).

To explore the hypothesis that women who are positive for thyroid autoantibodies have relative hypothyroidism, we meta-analysed the serum thyroid stimulating hormone concentrations in six studies. The weighted mean difference for thyroid stimulating hormone was significantly higher in the thyroid autoantibody positive group compared with the negative group by 0.51 mIU/L (95% confidence interval 0.14 to 0.88; $P=0.007$), giving credibility to this hypothesis (fig 5). There were insufficient data on serum free

thyroxine (fT4) and free triiodothyronine (T3) concentrations for meta-analysis.

Thyroid autoantibodies and preterm birth

Five studies^{28-30 43 44} including a total of 12 566 women evaluated the association between thyroid autoantibodies and preterm birth. All were cohort studies and had low risk of bias for selection and outcome assessment on the Newcastle-Ottawa scale.¹⁶ Three studies were judged to have medium risk of bias and two as high risk of bias for comparability of cohorts. All showed a positive association between the presence of thyroid autoantibodies and preterm births. Meta-analysis showed an increase in the odds of preterm birth in the presence of thyroid autoantibodies (2.07, 1.17 to 3.68; $P=0.01$) (fig 6).

Effect of levothyroxine treatment on pregnancy outcomes

Two randomised studies, including a total of 187 women, evaluated the effect of levothyroxine treatment on pregnancy outcomes.^{23 44} Both studies were in women with normal thyroid function with thyroid autoantibodies. One study was in unselected women⁴⁴ and the other in women scheduled to have in vitro fertilisation treatment.²³ One used levothyroxine at a dose of 1 $\mu\text{g/kg/day}$,²³ and the other used a titrated dose, with a mean levothyroxine dose of 49.7 $\mu\text{g/day}$ (SD 14 μg) in the treatment group.⁴⁴ The Jadad score¹⁷ for quality of the studies was 5/5 and 3/5. Both studies showed a reduction in miscarriage rates (36% and 75% relative reductions), and when the results were pooled, there was a significant 52% relative risk reduction in miscarriages with levothyroxine (0.48, 0.25 to 0.92; $P=0.03$) (fig 7). One of the two studies reported on preterm birth⁴⁴; this study ($n=115$) found a 69% relative risk reduction in preterm births with levothyroxine (0.31, 0.11 to 0.90).

DISCUSSION

Association of thyroid autoantibodies with adverse pregnancy outcomes

Our systematic review and meta-analysis of the published literature showed that in women with normal

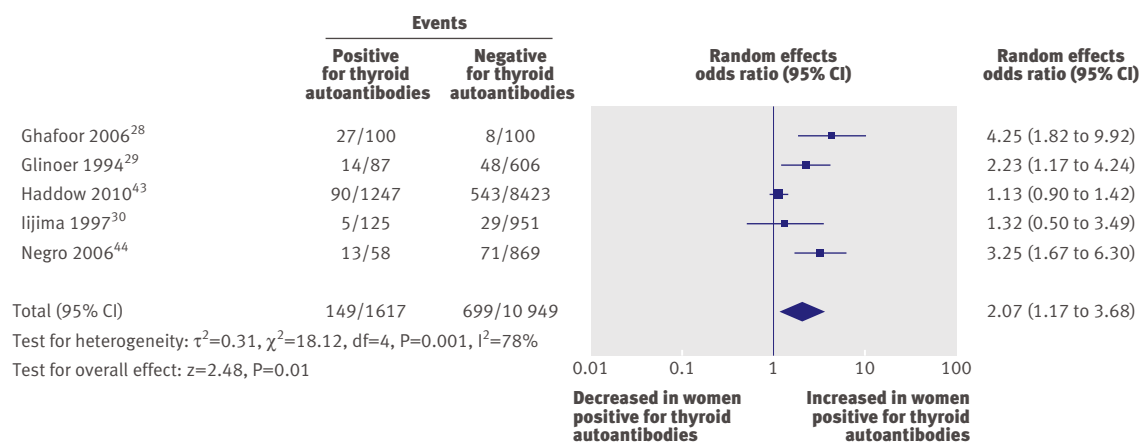


Fig 6 | Association between thyroid autoantibodies and preterm births

thyroid function, there is a strong association between the presence of thyroid autoantibodies and poor obstetric outcomes, for both miscarriage and preterm birth. The odds of miscarriage more than tripled and that of preterm birth doubled in women with thyroid autoantibodies.

Given the high prevalence of thyroid autoantibodies in women of reproductive age group, these increases in miscarriage and preterm birth are clinically highly relevant at the individual and population level. We showed that the increase in miscarriage rates in women positive for thyroid autoantibodies could not be accounted for by confounding factors such as a difference in age. Our review of the effectiveness of treatment with levothyroxine has provided preliminary evidence on its efficacy in reducing the rates of miscarriages and preterm births.

Five reviews have examined the association between thyroid autoantibodies and miscarriage,^{4,5 14 45 46} and one has examined the association with preterm birth.⁴⁷ Several new studies have emerged since these reviews were completed, however, and the existing reviews have used limited meta-analytical methods, necessitating our review.

Pathogenesis of adverse pregnancy outcomes with thyroid autoantibodies

The frequent presence of thyroid autoantibodies in several non-thyroidal autoimmune diseases supports a hypothesis of global immune dysfunction being relevant to these clinical outcomes.⁴⁸ There is evidence that there is an alteration in cytokine expression by peripheral T lymphocytes in women positive for thyroid antibodies outside of pregnancy.⁴⁹ Pregnancy is an inflammatory process involving a shift in the regulation of cytokine networks within the local placental-decidual environment.⁵⁰ Dysregulation of local inflammatory processes can be associated with miscarriage and premature delivery.⁵¹ The presence of thyroid autoantibodies can reflect a generalised activation of the immune system and specifically a dysregulated activity of the immune system at the fetal-maternal interface. Thyroid hormones can directly influence angiogenic growth

factor and cytokine production^{52,53} as well as trophoblast proliferation, survival, and invasion.^{54,55} Furthermore, the presence of thyroid autoantibodies might be a marker of underlying subtle alteration in thyroid reserve. A reduction in the functional reserve of the thyroid gland associated with reduced adaptation to the physiological changes of pregnancy could contribute to minor changes in circulating thyroid hormone concentrations within the reference range.⁵⁶ The increase in thyroid stimulating hormone concentrations in euthyroid women with thyroid autoantibodies supports this hypothesis. There were insufficient data to identify any differences in the concentrations of triiodothyronine (T3) between the two groups. We postulate that treatment with levothyroxine might correct any relative deficiency of thyroid hormones and impact on both systemic immune regulation and the local placental-decidual environment.

Clinical implications of the findings

The prevalence of the thyroid autoantibodies in the included studies varied between 5.4% and 31%. The miscarriage rates ranged from 2.4% to 42.9%. The association between thyroid autoantibodies and miscarriage was consistently strong across varying rates of thyroid autoantibodies and miscarriages. The individual studies used various assays for thyroid peroxidase antibodies, each with different detection limits and thresholds for test positivity, which were usually predetermined by the assay manufacturer. The effect size does not seem to be related to the threshold concentrations of thyroid peroxidase antibodies.

Although 28 of the 31 miscarriage studies and all five preterm studies showed a positive association, there was still unexplained heterogeneity in the meta-analyses for both miscarriage and preterm birth. The clinical heterogeneity between the studies on the population, test assay platforms, and thresholds used and the quality features of the studies are likely to have contributed to the statistical heterogeneity observed.

The strength of inference on the effectiveness of levothyroxine is weakened by the small number of

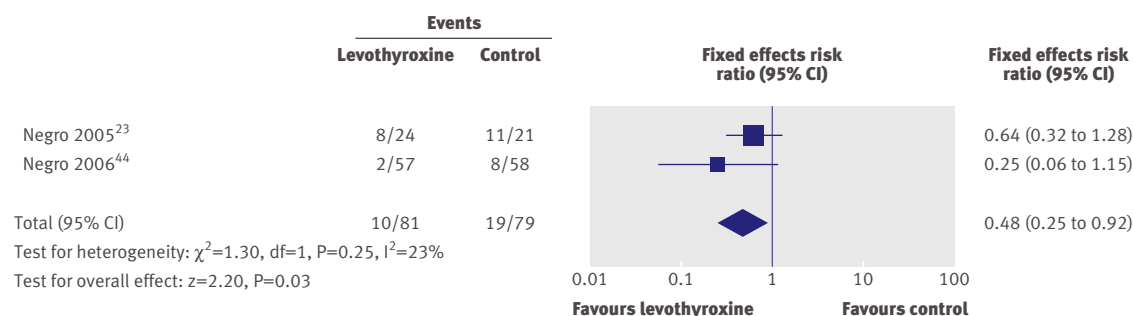


Fig 7 | Effect of levothyroxine treatment in reducing miscarriage in women with normal thyroid function and thyroid autoantibodies

studies. There have been only two small randomised trials involving a total of 187 women. One of them was not placebo controlled. To obtain a definitive answer on the role of levothyroxine in reducing miscarriages and preterm births a large placebo controlled randomised trial is needed with live births as the primary outcome. The two randomised studies included in the review did not find any safety concerns for the mother or the baby; specifically there were no instances of hyperthyroidism (resulting from overtreatment with levothyroxine). As the randomised trials were small and the follow-up was only to the end of pregnancy, however, these trials were not suitable for assessing rare or long term adverse events. Furthermore, the two trials on this topic have been conducted in the same research unit, with possible implications to the generalisability of the findings.

Contributors: AC conceived the review. EK, ST, and AT performed the search, study selection, and data extraction. ST, AT, and AC analysed the results. ST, AC, JF, and MDK drafted the manuscript. All authors provided input into the development of the manuscript. All authors have approved the final manuscript. AC is guarantor.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. The authors have been funded by the NIHR (National Institute of Health Research, UK) EME Programme (09-100-10) to conduct a multicentre placebo-controlled randomised trial on the pregnancy effects of levothyroxine treatment in thyroid antibody positive women with normal thyroid function (the TABLET trial).

Ethical approval: Not required.

Data sharing: No additional data available.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Thyroid autoantibodies are relatively common in women of reproductive age

Thyroid autoimmunity might be associated with adverse pregnancy outcomes

WHAT THIS STUDY ADDS

In women with normal thyroid function and thyroid autoantibodies the risk of miscarriage is more than tripled and the risk of preterm birth is doubled

Treatment with levothyroxine can halve the risk of miscarriage in women with normal thyroid function and thyroid autoantibodies

- NHS Direct Wales Encyclopaedia. Miscarriage. 2010. www.nhsdirect.wales.nhs.uk/encyclopaedia/m/article/miscarriage/.
- Creasy RK. Preventing preterm birth. *N Engl J Med* 1991;325:727-9.
- Mangham LJ, Petrou S, Doyle LW, Draper ES, Marlow N. The cost of preterm birth throughout childhood in England and Wales. *Pediatrics* 2009;123:e312-27.
- Stagnaro-Green A, Glinioer D. Thyroid autoimmunity and the risk of miscarriage. *Best Pract Res Clin Endocrinol Metab* 2004;18:167-81.
- Poppe K, Velkeniers B, Glinioer D. The role of thyroid autoimmunity in fertility and pregnancy. *Nat Clin Pract Endocrinol Metab* 2008;4:394-405.
- Bussen S, Steck T. Thyroid autoantibodies in euthyroid non-pregnant women with recurrent spontaneous abortions. *Hum Reprod* 1995;10:2938-40.
- Kutteh WH, Yetman DL, Carr AC, Beck LA, Scott RT Jr. Increased prevalence of antithyroid antibodies identified in women with recurrent pregnancy loss but not in women undergoing assisted reproduction. *Fertil Steril* 1999;71:843-8.
- Pratt D, Novotny M, Kaberlein G, Dudkiewicz A, Gleicher N. Antithyroid antibodies and the association with non-organ-specific antibodies in recurrent pregnancy loss. *Am J Obstet Gynecol* 1993;168:837-41.
- Kim CH, Chae HD, Kang BM, Chang YS. Influence of antithyroid antibodies in euthyroid women on in vitro fertilization-embryo transfer outcome. *Am J Reprod Immunol* 1998;40:2-8.
- Muller AF, Verhoeff A, Mantel MJ, Berghout A. Thyroid autoimmunity and abortion: a prospective study in women undergoing in vitro fertilization. *Fertil Steril* 1999;71:30-4.
- Negro R, Formoso G, Coppola L, Presicce G, Mangieri T, Pezzarossa A, et al. Euthyroid women with autoimmune disease undergoing assisted reproduction technologies: the role of autoimmunity and thyroid function. *J Endocrinol Invest* 2007;30:3-8.
- Glinioer D, Soto MF, Bourdoux P, Lejeune B, Delange F, Lemone M, et al. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. *J Clin Endocrinol Metab* 1991;73:421-7.
- Glinioer D, Delange F. The potential repercussions of maternal, fetal, and neonatal hypothyroxinemia on the progeny. *Thyroid* 2000;10:871-87.
- Prummel MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. *Eur J Endocrinol* 2004;150:751-5.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of non-randomised studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
- Review Manager (RevMan) [computer program]. Version 5.0. Cochrane Collaboration, 2008.
- StataCorp. Stata statistical software: release 10. StataCorp, 2007.
- De Carolis C, Greco E, Guarino MD, Perricone C, Dal LA, Giacomelli R, et al. Anti-thyroid antibodies and antiphospholipid syndrome: evidence of reduced fecundity and of poor pregnancy outcome in recurrent spontaneous aborters. *Am J Reprod Immunol* 2004;52:263-6.
- Pratt DE, Kaberlein G, Dudkiewicz A, Karande V, Gleicher N. The association of antithyroid antibodies in euthyroid nonpregnant women with recurrent first trimester abortions in the next pregnancy. *Fertil Steril* 1993;60:1001-5.

- 22 Rushworth FH, Backos M, Rai R, Chilcott IT, Baxter N, Regan L. Prospective pregnancy outcome in untreated recurrent miscarriers with thyroid autoantibodies. *Hum Reprod* 2000;15:1637-9.
- 23 Negro R, Mangieri T, Coppola L, Presicce G, Casavola EC, Gismondi R, et al. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. *Hum Reprod* 2005;20:1529-33.
- 24 Poppe K, Glinoe D, Tournaye H, Devroey P, van Steirteghem A, Kaufman L, et al. Assisted reproduction and thyroid autoimmunity: an unfortunate combination? *J Clin Endocrinol Metab* 2003;88:4149-52.
- 25 Poppe K, Glinoe D, Tournaye H, Schiettecatte J, Devroey P, van Steirteghem A, et al. Impact of ovarian hyperstimulation on thyroid function in women with and without thyroid autoimmunity. *J Clin Endocrinol Metab* 2004;89:3808-12.
- 26 Singh A, Dantas ZN, Stone SC, Asch RH. Presence of thyroid antibodies in early reproductive failure: biochemical versus clinical pregnancies. *Fertil Steril* 1995;63:277-81.
- 27 Bagis T, Gokcel A, Saygili ES. Autoimmune thyroid disease in pregnancy and the postpartum period: relationship to spontaneous abortion. *Thyroid* 2001;11:1049-53.
- 28 Ghafoor F, Mansoor M, Malik T, Malik MS, Khan AU, Edwards R, et al. Role of thyroid peroxidase antibodies in the outcome of pregnancy. *J Coll Physicians Surg Pak* 2006;16:468-71.
- 29 Glinoe D, Riahi M, Grun JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. *J Clin Endocrinol Metab* 1994;79:197-204.
- 30 Iijima T, Tada H, Hidaka Y, Mitsuda N, Murata Y, Amino N. Effects of autoantibodies on the course of pregnancy and fetal growth. *Obstet Gynecol* 1997;90:364-9.
- 31 Lejeune B, Grun JP, de Nayer P, Servais G, Glinoe D. Antithyroid antibodies underlying thyroid abnormalities and miscarriage or pregnancy induced hypertension. *Br J Obstet Gynaecol* 1993;100:669-72.
- 32 Sezer K, Kamel N, Unlu C, Celik HK. Impact of first trimester and postpartum period thyroid autoantibodies on abortion incidence in Turkish pregnant women. *Gynecol Endocrinol* 2009;25:387-91.
- 33 Sieiro Netto L, Medina CC, Micmacher E, Mamede Da Costa S, Nazar L, Galvao D, et al. Influence of thyroid autoimmunity and maternal age on the risk of miscarriage. *Am J Reprod Immunol* 2004;52:312-6.
- 34 Stagnaro-Green A, Roman SH, Cobin RH, el-Harazy E, Alvarez-Marfany M, Davies TF. Detection of at-risk pregnancy by means of highly sensitive assays for thyroid autoantibodies. *JAMA* 1990;264:1422-5.
- 35 Bellver J, Soares SR, Alvarez C, Munoz E, Ramirez A, Rubio C, et al. The role of thrombophilia and thyroid autoimmunity in unexplained infertility, implantation failure and recurrent spontaneous abortion. *Hum Reprod* 2008;23:278-84.
- 36 Bussen SS, Steck T. Thyroid antibodies and their relation to antithrombin antibodies, anticardiolipin antibodies and lupus anticoagulant in women with recurrent spontaneous abortions (antithyroid, anticardiolipin and antithrombin autoantibodies and lupus anticoagulant in habitual aborters). *Eur J Obstet Gynecol Reprod Biol* 1997;74:139-43.
- 37 Dendrinis S, Papasteriades C, Tarassi K, Christodoulakos G, Prasinos G, Creatsas G. Thyroid autoimmunity in patients with recurrent spontaneous miscarriages. *Gynecol Endocrinol* 2000;14:270-4.
- 38 Esplin MS, Branch DW, Silver R, Stagnaro-Green A. Thyroid autoantibodies are not associated with recurrent pregnancy loss. *Am J Obstet Gynecol* 1998;179:1583-6.
- 39 Irvani AT, Saeedi MM, Pakraves J, Hamidi S, Abbasi M. Thyroid autoimmunity and recurrent spontaneous abortion in Iran: a case-control study. *Endocr Pract* 2008;14:458-64.
- 40 Mecacci F, Parette E, Cioni R, Lucchetti R, Magrini A, La Torre P, et al. Thyroid autoimmunity and its association with non-organ-specific antibodies and subclinical alterations of thyroid function in women with a history of pregnancy loss or preeclampsia. *J Reprod Immunol* 2000;46:39-50.
- 41 Shoenfeld Y, Carp HJ, Molina V, Blank M, Cervera R, Balasch J, et al. Autoantibodies and prediction of reproductive failure. *Am J Reprod Immunol* 2006;56:337-44.
- 42 Nybo Anderson A. Maternal age and fetal loss: population based register linkage study. *BMJ* 2000;320:1708-12.
- 43 Haddow JE, Cleary-Goldman J, McClain MR, Palomaki GE, Neveux LM, Lambert-Messerlian G, et al. Thyroperoxidase and thyroglobulin antibodies in early pregnancy and preterm delivery. *Obstet Gynecol* 2010;116:58-62.
- 44 Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab* 2006;91:2587-91.
- 45 Chen L, Hu R. Thyroid autoimmunity and miscarriage: a meta-analysis. *Clin Endocrinol (Oxf)* 2011;74:513-9.
- 46 Toulis KA, Goulis DG, Venetis CA, Kolibianakis EM, Negro R, Tarlatzis BC, et al. Risk of spontaneous miscarriage in euthyroid women with thyroid autoimmunity undergoing IVF: a meta-analysis. *Eur J Endocrinol* 2010;162:643-52.
- 47 Stagnaro-Green A. Maternal thyroid disease and preterm delivery. *J Clin Endocrinol Metab* 2009;94:21-5.
- 48 Nakamura H, Usa T, Motomura M, Ichikawa T, Nakao K, Kawasaki E, et al. Prevalence of interrelated autoantibodies in thyroid diseases and autoimmune disorders. *J Endocrinol Invest* 2008;31:861-5.
- 49 Colin IM, Isaac J, Dupret P, Ledant T, D'Hautcourt JL. Functional lymphocyte subset assessment of the Th1/Th2 profile in patients with autoimmune thyroiditis by flowcytometric analysis of peripheral lymphocytes. *J Biol Regul Homeost Agents* 2004;18:72-6.
- 50 Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science* 2005;308:1592-4.
- 51 Challis JR, Lockwood CJ, Myatt L, Norman JE, Strauss JF III, Petraglia F. Inflammation and pregnancy. *Reprod Sci* 2009;16:206-15.
- 52 Mascanfroni I, Montesinos MM, Susperregui S, Cervi L, Ilarregui JM, Ramseyer VD, et al. Control of dendritic cell maturation and function by triiodothyronine. *FASEB J* 2008;22:1032-42.
- 53 Matsuo H, Maruo T, Murata K, Mochizuki M. Human early placental trophoblasts produce an epidermal growth factor-like substance in synergy with thyroid hormone. *Acta Endocrinol (Copenh)* 1993;128:225-9.
- 54 Barber KJ, Franklyn JA, McCabe CJ, Khanim FL, Bulmer JN, Whitley GS, et al. The in vitro effects of triiodothyronine on epidermal growth factor-induced trophoblast function. *J Clin Endocrinol Metab* 2005;90:1655-61.
- 55 Oki N, Matsuo H, Nakago S, Murakoshi H, Laoag-Fernandez JB, Maruo T. Effects of 3,5,3'-triiodothyronine on the invasive potential and the expression of integrins and matrix metalloproteinases in cultured early placental extravillous trophoblasts. *J Clin Endocrinol Metab* 2004;89:5213-21.
- 56 Glinoe D. Miscarriage in women with positive anti-TPO antibodies: is thyroxine the answer? *J Clin Endocrinol Metab* 2006;91:2500-2.

Accepted: 2 March 2011

Appendix 1 Clinical characteristics of the studies included in the systematic review of pregnancy outcomes in euthyroid women with thyroid auto-antibodies [posted as supplied by author]

a) Cohort studies

Study (Year) Language	Study		Population				Test				Outcome
	Quality	Number of patients	Prevalence of thyroid auto-antibodies	Inclusion criteria	Exclusion criteria	Any intervention	Description of test	Timing of testing	Frequency of testing	Cut off level	
DeCarolís (2004) English	Cohort Prospective Unreported patient enrolment Not blind Population described Test described Complete follow up	203 non-pregnant women with primary anti-phospholipid syndrome 162 controls	18.9%	203 non-pregnant women with primary antiphospholipid syndrome (antiphospholipid antibodies and recurrent miscarriage) Control group- 162 non-pregnant women with recurrent miscarriage and negative thyroid autoimmunity and antiphospholipid antibodies	Other possible causes of recurrent miscarriage (genetic, anatomic, hormonal, etc), autoimmune disease (except antiphospholipid positive)	High dose intravenous immunoglobulin (IVIg) (Flebogamma, Grifols, Pisa, Italy) once pregnancy is confirmed by a positive serum BHCG and gestational sac on ultrasound	Incomplete, Thyroid peroxidase (TPO) and Thyroglobulin (TG)-radioimmunoassay	Non pregnant-not specified the time of test in relation to last pregnancy	Once	Positive TPO >80 IU/ml, Positive TG > 80 IU/ml	Miscarriage
Pratt (1993) English	Cohort Prospective Unreported patient enrolment Not blind Population described Test described Outcome described Complete follow up	42 non-pregnant women with recurrent miscarriage	31.0%	Non-pregnant women with ≥ 3 consecutive pregnancy losses	Women with other obvious causes for pregnancy loss-significant uterine anomalies, uterine myomas, parental chromosomal abnormalities, autoimmune abnormalities among phospholipid antibodies	Patients with possible luteal phase defect with progesterone	Complete, TPO and TG- Kalibre Radio ImmunE Assay (RIA) kits	≥ 6 months pre pregnancy and 4 to 6 weeks from last menstrual period as pregnancy is diagnosed from rising hCG (human chorionic gonadotrophin)	2 times	Cut off not stated, but range of levels given and absolute levels for antibody positive, associated normal TSH 0.35-7.0 microIU/ml, associated normal fT4 0.9-2.1 ng/dl	First trimester miscarriage
Rushworth (2000) English	Cohort Prospective Consecutive patient enrolment Not blind Test described Outcome not described Follow up not complete	870 with recurrent miscarriages 105 pregnancies	22.9%	Attending recurrent miscarriage clinic, 3 or more miscarriages	Couples with abnormal karyotype, thyroid dysfunction, maternal history of thyroid dysfunction-although treated	None	TPO- Serodia ATM, TG- Japanese Serodia ATG particle agglutination kits	Pre pregnancy	Once	TG 1 in 100, TPO 1 in 400, associated normal TSH 0.5-5.0 mIU/l	First and second trimester miscarriage
Kim (1998) English	Cohort Prospective	28 euthyroid infertile	22.2%	Tubal factor or unexplained	Positive antinuclear	None	Inconclusive, TPO and TG-	6 months pre pregnancy	Once	Positive TPO>100 U/ml,	Miscarriage

	Unreported patient enrolment Not blind Complete follow up	women with antithyroid antibodies (cases) and 51 controls		infertility Control group- euthyroid women without antithyroid antibodies who underwent in vitro fertilisation (IVF) & embryo transfer (ET) (IVF-ET Embryo transfer)	antibody, lupus coagulant, anticardiolipin antibody or rheumatoid factor		radioligand assay			Positive TG >100 U/ml	
Muller (1999) English	Cohort Prospective Arbitrary patient enrolment Not blind Test described Outcome described Complete follow up	173 final patients consented (54 became pregnant)	22.2%	Attending IVF (Invitro fertiliSation) program	No consent, unable to determine if TPO antibodies were present	None	TPO- RIA (Radio immune assay)	Pre pregnancy, after miscarriage or within first trimester pregnancy if ongoing pregnancy	1-2 times	Positive TPO > 80 U/ml, associated normal TSH 0.2-4.5 microIU/ml	Miscarriage
Negro (2005) English	Cohort Prospective Unreported patient enrolment Blinding Test described Complete follow up	484 infertile women undergoing assisted reproductive technology (ART)- 72 TPO positive (of which 36 in Group A (treatment) and 36 in Group B (placebo) The other 412 in Group C- TPO negative	6.2%	Infertile women undergoing a first assisted reproduction technology, all patients underwent ovarian induction	Overt thyroid dysfunction	36 TPO patients (Group A) underwent levothyroxine (LT4) treatment 1 month before ART and throughout pregnancy	TPO- radioimmunoassay kit	Pre pregnancy (before undergoing ART), Thyroid Function Tests (TFTs) checked on Group A patients 1 month after LT4 started and before starting ART	Once	Positive TPO >100 kIU/l, associated normal TSH 0.27-4.2 mIU/l, associated normal fT4 9.3-18.0 ng/l (12-33.5 pmol/l)	Miscarriage rates (included early pregnancy loss- biochemical) Pregnancy rates Delivery rates
Negro (2006) English	Cohort Retrospective Unreported patient enrolment Not blind Test described	255 infertile women who underwent assisted reproductive technology	6.3%	Infertile women undergoing first ART procedure during study period	Women > 35 years of age, overt thyroid dysfunction	None	TPO- RIA kit	TPO and TFTs checked before ART, then TFTs at 12 and 30 weeks gestation	Once	Positive TPO >100 kIU/l, associated normal TSH 0.27-4.2 mIU/l, associated normal fT4 9.3-18.0 ng/l (12-33.5 pmol/l)	Delivery rate Pregnancy Miscarriage
Poppe (2003) English	Cohort Prospective Unreported patient enrolment Not blind Complete follow up	234 infertile female patients	16.3%	Attending Center for Reproductive Medicine before a first ART cycle, all patients received controlled ovarian superovulation	Overt thyroid dysfunction	None	TPO- RIA kit	Pre pregnancy & pre ART	Once	Positive TPO >100 kIU/l, normal TSH 0.27-4.2 mIU/l, normal fT4 9.3-18.0 ng/l (12-33.5 pmol/l)	Miscarriage

Poppe (2004) English	Cohort Prospective Unreported patient enrolment Not blind Population described Test described Outcome described Complete follow up	35 infertile, post-ovarian hyperstimulation women	25.7%	Infertile, euthyroid women with an ongoing pregnancy after having ovarian hyperstimulation	Not mentioned	None	Complete, TPO-RIA kit (B.R.A.H.M.S. Diagnostica, Berlin)	>20 days before a first assisted reproductive technology (ART), then TFTs monitored every 20 days after ovulation induction during first trimester	Once	Positive TPO >100 kU/l, associated normal TSH 0.27-4.2 mU/L, associated normal fT4 9.3-18.0 ng/liter (12-23.2 pmol/l)	First trimester miscarriage
Singh (1995) English	Cohort Retrospective Unreported patient enrolment Not blind Test described Complete follow up	487 infertile patients who conceived with ART	21.8%	Successfully conceived with assisted reproductive techniques (ART)	None	None	Inconclusive, TPO & TG- enzyme immunoassay	Stored serum- 14 day post embryo transfer (hCG >5)	Once	Index ratio compared to patient- reflects ratio of patient specimen absorbance to the absorbance of a positive reference, positive sample antibody index ≥ 3.8	Miscarriage (clinical, biochemical, ectopic pregnancy), delivered
Bagis (2001) English	Cohort Retrospective Unreported patient enrolment Not blind Test described	902 women consented, 876 completed the study	12.3%	First visit to the antenatal clinics, no history of thyroid disorder, women who had been seen at least twice in the postpartum period	Without consent, abnormal thyroid function	None	TPO & TG- IMMULITE autoanalyser using a chemi luminescent enzyme immunometric assay	12 weeks, between 32 to 36 weeks, and then every 2 months postpartum until 1 year after delivery	8 times	Positive TPO >35 IU/ml, positive TG >40 iu/ml, associated normal TSH 0.3-4.0 microU/ml, associated normal fT4 9-25 pmol/ml	Recurrent miscarriage 1 year post partum follow up
Ghafoor (2006) English	Cross-sectional Prospective Unreported patient enrolment Not blind Population described Test described Outcome described Complete follow up	1500 euthyroid pregnant women	11.2%	All euthyroid pregnant women registered at antenatal clinic, aged 18-40	Not mentioned	None	TPO – ELISA, inhouse assay reagents FT4 & TSH- ELISA kits	Not mentioned	Once	Positive TPO > 100 U/ml	Miscarriage Preterm livery
Glincoer (1991) English	Cohort Prospective Not blind Population described Test described	726 pregnant women	6.9%	Euthyroid, pregnant women	Overt thyroid dysfunction thyroid autoimmunity, goiter, nodules or past thyroid	None	TG- solid phase RIA TPO- DYNO-test anti-TPO kit	<20 weeks in more than 70% of pregnancies, at 32 weeks gestation, 3 days after	3 times	Positive TG >30 microg/L, Positive TPO >100 U/ml	Miscarriage

	Complete follow up			disorder			delivery				
Glinioer (1994) English	Cohort Prospective Consecutive patient enrolment Not blind Test described Complete follow up	87 euthyroid women & positive thyroid antibodies (cases) Control group- 606 healthy pregnant women	12.6%	Consecutive euthyroid pregnant women attending prenatal clinic without previous history of thyroid disease, positive thyroid antibodies	Women with positive thyroid antibodies and abnormal thyroid function (hypo- and hyperthyroidism)	None	Complete, TPO-DYNO-test anti-TPO kit TG- RIA developed following the method of Delespesse	Each trimester and 3-4 days post delivery (sequential)	Sequential during gestation to parturition- 4 times	Positive TPO >150 U/ml, positive TG > 50 U/ml, associated normal TSH 0.2-4.0 mU/l	Miscarriage Preterm delivery Neonatal weight, height, cranial perimeter, Apgar score
Iijima (1997) English	Cohort Prospective Unreported patient enrolment Not blind Population described Test described Outcome described Complete follow up	1179 pregnant women	11.6%	Healthy pregnant women	Multifetal gestations, antiphospholipid autoantibodies or lupus anticoagulant	None	TPO & TG hemagglutination or particle aggregation kits	6 to 14 weeks gestation	Once	Positive TPO $\geq$ 1 in 100, Positive TG $\geq$ 1 in 100	Miscarriage Preterm delivery Pregnancy-induced hypertension Stillbirth Birth weight Any abnormalities
Lejeune (1993) English	Cohort Prospective Arbitrary patient enrolment	730 consecutive pregnant women	6.3%	Attending antenatal clinic- euthyroid pregnant women	Women not assessed < 14 weeks gestation	None	TG- solid phase RIA, TPO-DYNO-test anti-TPO kit	First trimester pregnancy	Not specified	Positive TG >100 U/ml, Positive TPO >150 U/ml	First and second trimester miscarriage Pregnancy induced hypertension
Sieiro Netto (2004) English	Cohort Prospective Unreported patient enrolment Not blind Test described Complete follow up	534 pregnant women	5.4%	Attended antenatal clinic- euthyroid, pregnant women	Overt thyroid dysfunction	None	Complete, TPO-ICMA method	During pregnancy	Once	Positive TPO >40 U/ml, associated normal TSH 0.4-3.8 mU/l, associated normal fT4 0.8-2.0 ng/dl	Miscarriage < weeks Live birth
Stagnaro-Green (1990) English	Cohort Prospective Consecutive patient enrolment Not blind Population described Test described	552 pregnant women	20.3%	First trimester pregnant women < 13 weeks	None	None	Complete, TPO and TG- specific sensitive ELISAs	6 to 13 weeks during pregnancy	Once	ELISA index reference, normal range for thyroid autoantibody ELISAs < 0.20, normal T4 58-161 nmol/l	First and second trimester miscarriage
Sezer (2009) English	Cohort Prospective	Euthyroid 128 pregnant	21.9%	All euthyroid women (aged 18-39) had a	Women with habitual	None	Serum TSH, free T ₄ , TPO and TG-	Once during first trimester of	Twice	Positive TPO >34 IU/ml,	Miscarriage, e births

	Population described Not blind Test described Outcome described Complete follow up	women		history of maximum one abortus without any previous endocrinological, immunological disorders.	miscarriage, miscarriage with known causes (anatomical defects, genetic abnormalities, autoimmune disorders) or in vitro fertilisation		Roche E170	gestation and 1 month after live birth or miscarriage		Positive TG > 115 IU/ml, normal TSH 0.3-4.5 mIU/l, normal free T ₄ 10-22 pmol/l	
Haddow (2010) English	Cross-sectional Prospective Unreported patient enrolment Not blind Population described Test described Outcome described Complete follow up	9670 euthyroid pregnant women, 392 hypothyroid pregnant women	14.6%	All euthyroid pregnant women registered at antenatal clinic, with viable single pregnancy. Thyroid related measurements were available in the first and second trimester and gestational age was established by ultrasonography. Included cohort was participants in the FaSTER First and Second Trimester Risk of Aneuploidy study.	Women with unknown hypothyroid status	None	TPO and TG measured using the Immulite 2000 methodology	Tests in first and second trimester	Twice	Positive TPO >35IU/ml Positive TG >40IU/ml	Preterm delivery <37 weeks and 32 weeks Birth weight < 2.5 kg Preterm Premature Rupture Of Membranes

b) Case-control studies

Study (Year) Language	Study			Population		Description of test	Test			Outcome
	Quality	Number of patients	Inclusion criteria	Exclusion criteria	Any intervention		Timing of testing	Frequency of testing	Cut off level	
Bellver (2008) English	Case-control Retrospective Unreported patient enrolment Population described Test described Outcome described Complete follow up	31 women with unexplained infertility, 26 women with implantation failure, 30 women with recurrent miscarriage (cases) 32 controls	Cases- less than 38 years of age, normal karyotype, normal ovarian function, normal uterus, no endocrine or autoimmune disorders, at least 2 clinical miscarriages Control group- 32 oocyte donors of 18-35 years of age, all Caucasian, with normal karyotype, no history of spontaneous abortion, autoimmune	Not mentioned	None	Complete, TPO & TG- 2-site immunoluminometric assay (sandwich principle)	>3 months post pregnancy	Once	Positive TPO >25 UI/ml, Positive TG >100 UI/ml	Recurrent miscarriage

			disorders or endocrine diseases, and previous term pregnancies without complications.							
Bussen (1995) English	Case-control Retrospective Unreported patient enrolment Not blind Population described Test described Outcome described Complete follow up	22 euthyroid, non pregnant women with recurrent miscarriage (cases), 44 controls without endocrine dysfunction	22 non-pregnant women with ≥ 3 consecutive pregnancy losses (only 2 women had 1 live birth before consecutive losses) Control group- random selection of women between 2 and 6 term pregnancies and had no history of previous abortions.	Significant uterine abnormalities or parental chromosomal abnormalities	None	Complete, TPO & TG- ELISA kits;	>6 months post pregnancy	Once	TPO >100 IU/ml, TG >100 IU/ml	Miscarriage
Bussen (1997) English	Case-control Retrospective Not blind Population described Test described Outcome described Complete follow up	28 Recurrent miscarriage (cases) 28 controls	Euthyroid non-pregnant habitual aborters (only 2 of 28 women had a live birth before their consecutive losses) Control group- multigravidae without previous abortions or endocrine dysfunctions	Systemic lupus erythematoses, uterine abnormalities, abnormal chromosome, autoimmune diseases	None	TPO & TG- ELISA kits	>6 months post pregnancy	Once	Positive TPO >100 IU/ml, Positive TG >100 IU/ml	Recurrent miscarriage
Dendrinios (2000) English	Case-control Retrospective Unreported patient enrolment Not blind Complete follow up	30 women with recurrent miscarriages (cases) and 15 controls	3 or more consecutive pregnancy losses Control group- fertile women with 1 to 2 live births	Known causes of recurrent miscarriages-	None	Inconclusive, TPO & TG- chemiluminescence sandwich immunoassay	>6 months post pregnancy	Once	Positive range for this assay >2 IU/ml, associated normal TSH 0.5-4.6 microIU/ml	Recurrent miscarriage
Esplin (1998) English	Case-control Retrospective Arbitrary patient enrolment Blinding Test described	74 non-pregnant women with recurrent miscarriage (cases) and 75 healthy controls	≥ 3 consecutive pregnancy losses with ≤ 1 previous live birth, negative lupus anticoagulant and < 20 IgG phospholipid binding units of anticardiolipin antibodies	Identifiable cause of pregnancy losses, pregnant within 6 months before included into study	Daily progesterone vaginal suppository if luteal-phase defect present	Complete, IgG TPO and IgG TG- radioimmunoassay kits	>6 months post pregnancy	Once	Not stated, associated normal TSH 0.2-5.0 microU/ml	Recurrent miscarriage
Iravani (2008) English	Case-control Retrospective Consecutive or arbitrary patient enrolment Not blind	641 patients with recurrent miscarriages (cases) and 296 controls	Recurrent miscarriage before 20 weeks and previous ≥ 3 consecutive miscarriages Control group-	Abnormal thyroid function tests, positive antiphospholipid antibodies,	None	Complete, TPO- ELISA TG- ELISA method	>6 months post pregnancy	Once	TG >125 IU/ml, TPO > 40 IU/ml, normal TSH 0.4-4 mIU/L, normal T4 4.5-	Recurrent miscarriage

	Population described Test described Outcome described Complete follow up		randomly recruited from women who had delivered during the study period	positive cervical culture, anatomic abnormalities, abnormal karyotype, abnormal hormonal profile and known or treated thyroid disease					10.9 microg/dL, normal T3 60-181 ng/dL	
Kutteh (1999) English	Case-control Retrospective Unreported patient enrolment Not blind Population described Test described Outcome described Complete follow up	688 infertile women undergoing ART (Assisted reproductive techniques), 700 women with recurrent miscarriage (cases), Control- 200 healthy women	Women undergoing assisted reproductive Women with at least 2 consecutive pregnancy losses (cases). Control group- healthy, non-pregnant, reproductive-aged, parous women without reproductive problems	Those undergoing ART with more than one pregnancy loss or known thyroid disease Those with ≥ 2 consecutive pregnancy losses and known thyroid disease	None	TPO and TG-ELISA tests kits	At least 3 months after pregnancy or miscarriage before ART cycles (pre pregnancy)	Once	Positive TPO ≥ 65 IU/ml Positive TG ≥ 120 IU/ml	Recurrent miscarriage
Mecacci (2000) English	Case-control Retrospective Unreported patient enrolment Not blind Population described Test described Outcome described Complete follow up	360 initially for Preconception counseling (PCC)- 69 cases and 69 control	Referrals for Pre conception counseling (history of recurrent miscarriage, fetal death or preeclampsia), 2 or more spontaneous miscarriage ≤ 12 weeks, ≥ 1 unexplained fetal death more than 12 weeks, BP more than 140/90 mmHg on 2 occasions 6 hours apart and proteinuria > 0.3 g/l/24 hour in previous gestations) Control group- no history of thyroid disorders or obstetric complications, age, gravidity and parity matched.	None	None	Inconclusive; TPO-RIA kits TG- RIA kits	>6 months post pregnancy	Once	TG >50 iu/ml, TPO >10 iu/ml, associated TSH, associated normal free T3 2.6-5.6 pg/ml and free T4 7.8-18.4 pg/ml	Recurrent miscarriage Pre-eclampsia Fetal death
Pratt (1993) English	Case-control Retrospective Unreported patient enrolment Not blind	45 women with recurrent miscarriage (cases) 100 controls	Women with recurrent miscarriage (3 or more consecutive first- or second- trimester losses)	Not mentioned	None	Complete, TPO and TG- Kalibre radioimmunoassay kits	Non pregnant- not specified the time of test in relation to last	Once	Positive TPO ≥ 0.3 U/ml, Positive TG ≥ 0.3 U/ml, associated normal TSH	Recurrent miscarriage

	Population described Test described Complete follow up		Control group- normal blood donors, aged 18-68 years				pregnancy		0.35-7.0 microIU/ml, associated normal fT4 0.9-2.1 ng/dl	
Shoenfeld (2006) English	Case-control Retrospective Unreported patient enrolment Complete follow up	269 non pregnant clinic (cases) – 109 recurrent pregnancy loss, 69 infertility, 3 infections, 5 ectopics, 63 unclassified pregnancy loss 120 controls	Cases- recurrent pregnancy loss (RPL), unclassified pregnancy loss, infertility, previous ectopic pregnancy, infections, autoimmune diseases. Patient attending gynaecology, immunology or obstetrics clinics Control group- healthy volunteers age-matched to the cases	Women being pregnant at the time of testing	None	Inconclusive, TG and TPO- enzyme- linked immunosorbent assay kits	Non pregnant- not specified the time of test in relation to last pregnancy	Once	Not stated	Recurrent miscarriage