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		Population					Test				Outcome
Study (Year) Language	**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**	
DeCarolis (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	PositiveTPO >100 kU/l, associated normal TSH 0.27-4.2 mU/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 kU/l, normal TSH 0.27-4.2 mU/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 $\geq$ 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
Glinoer (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			
Glinoer (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 livery Pregnancy-induced hypertension Stillbirth Birth weight Any lformations
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 luced pertension
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			Population			Test				Outcome
Study (Year) Language	**Quality**	**Number of patients**	**Inclusion criteria**	**Exclusion criteria**	**Any intervention**	**Description of test**	**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	28Recurrent 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 erythematodes, 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
Dendrinos (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 arbitary patient enrolment Not blind	641patients with recurrent miscarriages (cases) and 296 controls	Recurrent miscarriage before 20 weeks and previous ≥ 3 consecutive miscarriages Control group-	Abnormal thyroid function tests, positive antiphospholip id 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 >50iu/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