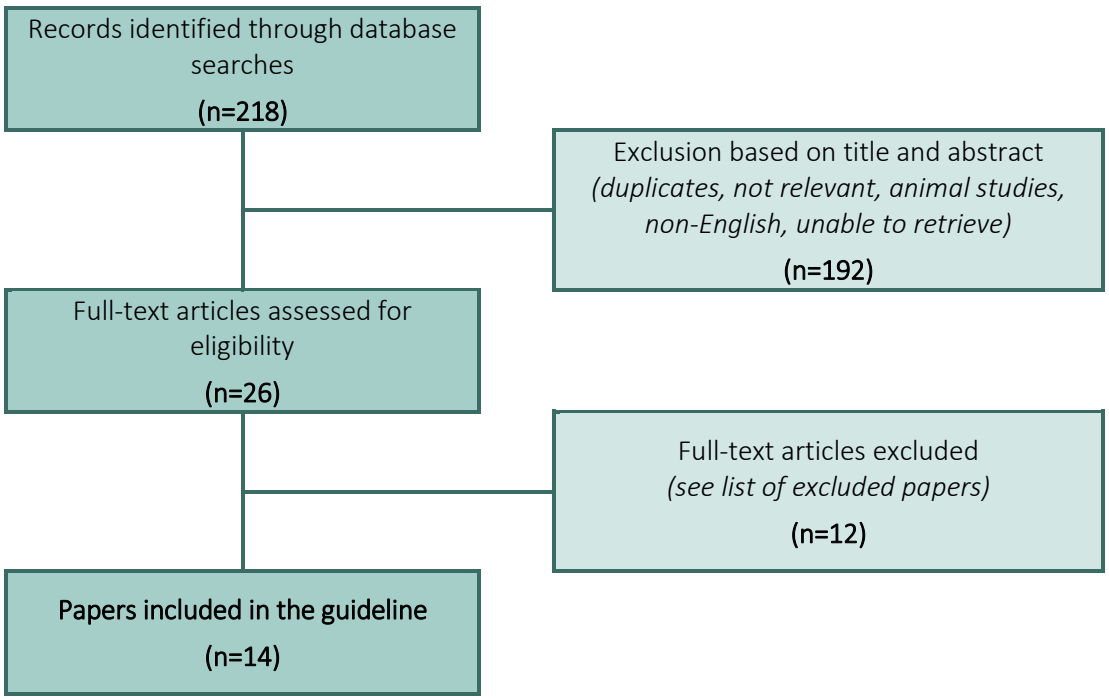
Annex 7: Literature study: flowcharts, list of excluded studies

1. Are health behaviour modifications relevant for reducing the risk of miscarriage in women with a history of RPL?

Flowchart

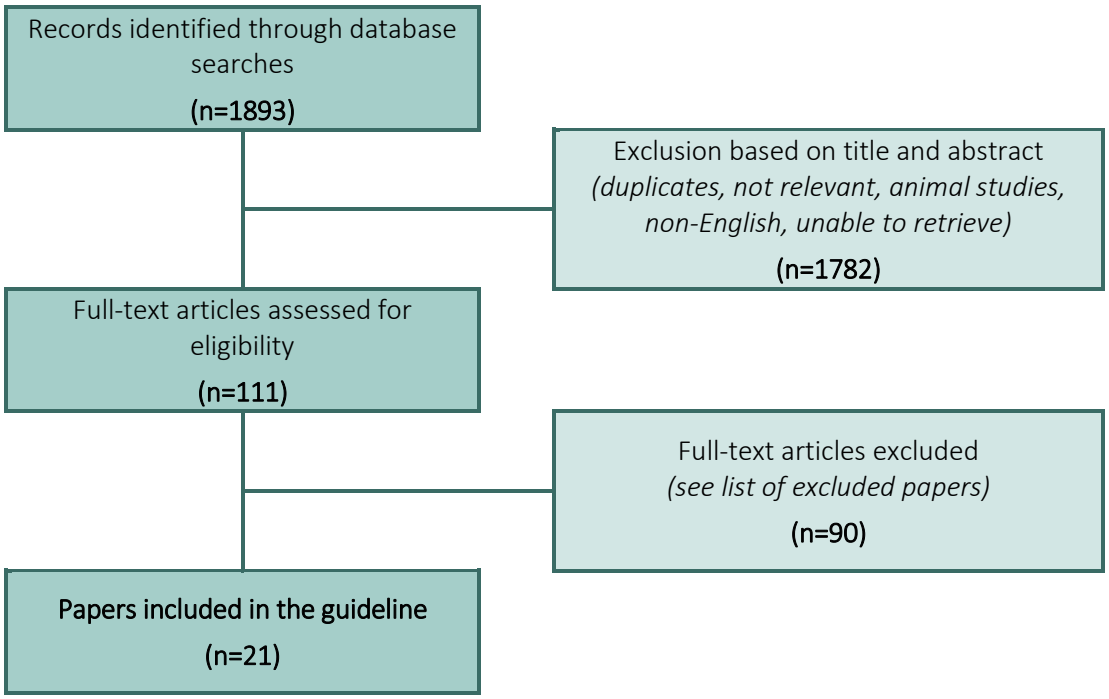


List of excluded papers

	EXCLUSION CRITERION
Bailey BA, Byrom AR. Factors predicting birth weight in a low-risk sample: the role of modifiable pregnancy health behaviors. Maternal and child health journal 2007;11: 173-179.	Not RPL
Benedict MD, Missmer SA, Vahratian A, Berry KF, Vitonis AF, Cramer DW, Meeker JD. Secondhand tobacco smoke exposure is associated with increased risk of failed implantation and reduced IVF success. Human reproduction 2011;26: 2525-2531.	Not RPL
Cavallo F, Russo R, Zotti C, Camerlengo A, Ruggenini AM. Moderate alcohol consumption and spontaneous abortion. Alcohol and alcoholism 1995;30: 195-201.	Not RPL
de Weerd S, Steegers-Theunissen RP, de Boo TM, Thomas CM, Steegers EA. Maternal periconceptional biochemical and hematological parameters, vitamin profiles and pregnancy outcome. European journal of clinical nutrition 2003;57: 1128-1134.	Not RPL
Derbyshire E, Abdula S. Habitual caffeine intake in women of childbearing age. Journal of human nutrition and dietetics 2008;21: 159-164.	Not RPL
Fedorcsak P, Storeng R, Dale PO, Tanbo T, Abyholm T. Obesity is a risk factor for early pregnancy loss after IVF or ICSI. Acta obstetricia et gynecologica Scandinavica 2000;79: 43-48.	Pregnancy loss after ART
Hebel JR, Nowicki P, Sexton M. The effect of antismoking intervention during pregnancy: an assessment of interactions with maternal characteristics American journal of epidemiology. 1985, pp. 135-148.	Not RPL
Henriksen TB, Hjollund NH, Jensen TK, Bonde JP, Andersson AM, Kolstad H, Ernst E, Giwercman A, Skakkebaek NE, Olsen J. Alcohol consumption at the time of conception and spontaneous abortion. American journal of epidemiology 2004;160: 661-667.	Not RPL
Jukic AM, Weinberg CR, Baird DD, Wilcox AJ. The association of maternal factors with delayed implantation and the initial rise of urinary human chorionic gonadotrophin. Human reproduction 2011;26: 920-926.	Not RPL
Juutilainen J, Hatfield T, Laara E. Evaluating alternative exposure indices in epidemiologic studies on extremely low-frequency magnetic fields. Bioelectromagnetics 1996;17: 138-143.	Not RPL
Kirkham C, Harris S, Grzybowski S. Evidence-based prenatal care: Part I. General prenatal care and counseling issues. American family physician 2005;71: 1307-1316.	Not RPL
Reindollar RH. Contemporary issues for spontaneous abortion. Does recurrent abortion exist? Obstetrics and gynecology clinics of North America 2000;27: 541-554.	Narrative

2. WHAT ARE THE KNOWN RISK FACTORS OF RPL?

Flowchart



List of excluded papers

	EXCLUSION CRITERION
Determinants of cervical Chlamydia trachomatis infection in Italy. The Italian MEGIC Group. Genitourinary medicine 1993;69: 123-125.	Chlamydia trachomatis infection
Absalan F, Ghannadi A, Kazerooni M, Parifar R, Jamalzadeh F, Amiri S. Value of sperm chromatin dispersion test in couples with unexplained recurrent abortion. Journal of assisted reproduction and genetics 2012;29: 11-14.	Semen quality – discussed in male factor chapter – excluded here
Ajayi OO, Charles-Davies MA, Arinola OG. Progesterone, selected heavy metals and micronutrients in pregnant Nigerian women with a history of recurrent spontaneous abortion. African health sciences 2012;12: 153-159.	too small to draw conclusions
Alijotas-Reig J, Garrido-Gimenez C. Current concepts and new trends in the diagnosis and management of recurrent miscarriage. Obstetrical & gynecological survey 2013;68: 445-466.	Review of unacceptable quality
Andalib A, Rezaie A, Oreizy F, Shafiei K, Baluchi S. A study on stress, depression and NK cytotoxic potential in women with recurrent spontaneous abortion. Iranian journal of allergy, asthma, and immunology 2006;5: 9-16.	stress versus immune system only not relevant
Baker VL, Luke B, Brown MB, Alvero R, Frattarelli JL, Usadi R, Grainger DA, Armstrong AY. Multivariate analysis of factors affecting probability of pregnancy and live birth with in vitro fertilization: an analysis of the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System. Fertility and sterility 2010;94: 1410-1416.	IVF
Baltaci V, Aygun N, Akyol D, Karakaya AE, Sardas S. Chromosomal aberrations and alkaline comet assay in families with habitual abortion. Mutation research 1998;417: 47-55.	Semen quality – discussed in male factor chapter – excluded here
Barraud-Lange V, Pont JC, Ziyyat A, Pocate K, Sifer C, Cedrin-Durnerin I, Fechtali B, Ducot B, Wolf JP. Seminal leukocytes are Good Samaritans for spermatozoa. Fertility and sterility 2011;96: 1315-1319.	Semen quality – discussed in male factor chapter – excluded here
Bellver J, Meseguer M, Muriel L, Garcia-Herrero S, Barreto MA, Garda AL, Remohi J, Pellicer A, Garrido N. Y chromosome microdeletions, sperm DNA fragmentation and sperm oxidative stress as causes of recurrent spontaneous abortion of unknown etiology. Human reproduction 2010;25: 1713-1721.	Semen quality – discussed in male factor chapter – excluded here
Bellver J, Rossal LP, Bosch E, Zuniga A, Corona JT, Melendez F, Gomez E, Simon C, Remohi J, Pellicer A. Obesity and the risk of spontaneous abortion after oocyte donation. Fertility and sterility 2003;79: 1136-1140.	Included in question 1
Bhattacharya SM. Association of various sperm parameters with unexplained repeated early pregnancy loss--which is most important? International urology and nephrology 2008;40: 391-395.	Semen quality – discussed in male factor chapter – excluded here
Bhattacharya SM. Hypo-osmotic swelling test and unexplained repeat early pregnancy loss. The journal of obstetrics and gynaecology research 2010;36: 119-122.	Semen quality – discussed in male factor chapter – excluded here
Boots C, Stephenson MD. Does obesity increase the risk of miscarriage in spontaneous conception: a systematic review. Seminars in reproductive medicine 2011;29: 507-513.	Included in question 1
Boots CE, Bernardi LA, Stephenson MD. Frequency of euploid miscarriage is increased in obese women with recurrent early pregnancy loss. Fertility and sterility 2014;102: 455-459.	Included in question 1
Brahem S, Mehdi M, Landolsi H, Mougou S, Elghezal H, Saad A. Semen parameters and sperm DNA fragmentation as causes of recurrent pregnancy loss. Urology 2011;78: 792-796.	Semen quality – discussed in male factor chapter – excluded here
Carrell DT, Liu L, Peterson CM, Jones KP, Hatasaka HH, Erickson L, Campbell B. Sperm DNA fragmentation is increased in couples with unexplained recurrent pregnancy loss. Archives of andrology 2003;49: 49-55.	Semen quality – discussed in male factor chapter – excluded here
Carrell DT, Wilcox AL, Lowy L, Peterson CM, Jones KP, Erickson L, Campbell B, Branch DW, Hatasaka HH. Elevated sperm chromosome aneuploidy and apoptosis in patients with unexplained recurrent pregnancy loss. Obstetrics and gynecology 2003;101: 1229-1235.	Semen quality – discussed in male factor chapter – excluded here

Chaichian S, Shoaee S, Saremi A, Pedar S, Firouzi F. Factors influencing success rate of leukocyte immunization and anti-paternal antibodies in spontaneous recurrent miscarriage. American journal of reproductive immunology 2007;57: 169-176.	history of infectious disease only
Chakraborty P, Goswami SK, Rajani S, Sharma S, Kabir SN, Chakravarty B, Jana K. Recurrent pregnancy loss in polycystic ovary syndrome: role of hyperhomocysteinemia and insulin resistance. PloS one 2013;8: e64446.	case control both groups have PCOS
Chen ZJ, Shi Y. Polycystic ovary syndrome. Frontiers of medicine in China 2010;4: 280-284.	Review of unacceptable quality
Clifford K, Rai R, Watson H, Regan L. An informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases. Human reproduction 1994;9: 1328-1332.	500 women with RM no control
Collodel G, Giannerini V, Antonio Pascarelli N, Federico MG, Comodo F, Moretti E. TEM and FISH studies in sperm from men of couples with recurrent pregnancy loss. Andrologia 2009;41: 352-360.	not about environmental exposure
Coughlan C, Walters S, Ledger W, Li TC. A comparison of psychological stress among women with and without reproductive failure. International journal of gynaecology and obstetrics 2014;124: 143-147.	RPL versus RIF
Craig M. Stress and recurrent miscarriage. Stress (Amsterdam, Netherlands) 2001;4: 205-213.	Included studies too poor to draw conclusions
de Weerd S, Steegers-Theunissen RP, de Boo TM, Thomas CM, Steegers EA. Maternal periconceptional biochemical and hematological parameters, vitamin profiles and pregnancy outcome. European journal of clinical nutrition 2003;57: 1128-1134.	Not relevant for the question
Diejomaoh M, Jirous J, Al-Azemi M, Baig S, Gupta M, Tallat A. The relationship of recurrent spontaneous miscarriage with reproductive failure. Medical principles and practice : international journal of the Kuwait University, Health Science Centre 2003;12: 107-111.	No controls
Diejomaoh MF, Al-Azemi M, Jirous J, Bandar A, Egbase P, Al-Sweih N, Al-Othman S. The aetiology and pattern of recurrent pregnancy loss. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 2002;22: 62-67.	No controls
Fedorcsak P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, Omland AK, Abyholm T, Tanbo T. Impact of overweight and underweight on assisted reproduction treatment. Human reproduction 2004;19: 2523-2528.	ART
Fedorcsak P, Storeng R, Dale PO, Tanbo T, Abyholm T. Obesity is a risk factor for early pregnancy loss after IVF or ICSI. Acta obstetricia et gynecologica Scandinavica 2000;79: 43-48.	obesity independent risk factor for miscarriage in IVF patients
Fraga CG, Motchnik PA, Wyrobek AJ, Rempel DM, Ames BN. Smoking and low antioxidant levels increase oxidative damage to sperm DNA. Mutation research 1996;351: 199-203.	sperm damage not miscarriage
Furness DL, Dekker GA, Roberts CT. DNA damage and health in pregnancy. Journal of reproductive immunology 2011;89: 153-162.	review article not other papers quoted opinion that toxins probably important only
Gerhard I, Daniel V, Link S, Monga B, Runnebaum B. Chlorinated hydrocarbons in women with repeated miscarriages. Environmental health perspectives 1998;106: 675-681.	no adequate controls
Gil-Villa AM, Cardona-Maya W, Agarwal A, Sharma R, Cadavid A. Assessment of sperm factors possibly involved in early recurrent pregnancy loss. Fertility and sterility 2010;94: 1465-1472.	Semen quality – discussed in male factor chapter – excluded here
Glueck CJ, Wang P, Bornovali S, Goldenberg N, Sieve L. Polycystic ovary syndrome, the G1691A factor V Leiden mutation, and plasminogen activator inhibitor activity: associations with recurrent pregnancy loss. Metabolism: clinical and experimental 2003;52: 1627-1632.	Similar to Glueck 2004
Glueck CJ, Wang P, Goldenberg N, Sieve L. Pregnancy loss, polycystic ovary syndrome, thrombophilia, hypofibrinolysis, enoxaparin, metformin. Clinical and applied thrombosis/hemostasis 2004;10: 323-334.	24 women with multiple treatments
Gopalkrishnan K, Padwal V, Meherji PK, Gokral JS, Shah R, Juneja HS. Poor quality of sperm as it affects repeated early pregnancy loss. Archives of andrology 2000;45: 111-117.	Semen quality – discussed in male factor chapter – excluded here
Hakim RB, Gray RH, Zacur H. Infertility and early pregnancy loss. American journal of obstetrics and gynecology 1995;172: 1510-1517.	148 women trying spontaneous pregnancy: not relevant

Homburg R. Pregnancy complications in PCOS. Best practice & research Clinical endocrinology & metabolism 2006;20: 281-292.	pcos
Hourvitz A, Lerner-Geva L, Elizur SE, Baum M, Levron J, David B, Meirow D, Yaron R, Dor J. Role of embryo quality in predicting early pregnancy loss following assisted reproductive technology. Reproductive biomedicine online 2006;13: 504-509.	After IVF, not RPL
Johnson P, Pearce JM. Recurrent spontaneous abortion and polycystic ovarian disease: comparison of two regimens to induce ovulation. BMJ 1990;300: 154-156.	treatment
Kazerooni T, Asadi N, Jadid L, Kazerooni M, Ghanadi A, Ghaffarpasand F, Kazerooni Y, Zolghadr J. Evaluation of sperm's chromatin quality with acridine orange test, chromomycin A3 and aniline blue staining in couples with unexplained recurrent abortion. Journal of assisted reproduction and genetics 2009;26: 591-596.	test rather than association
Ke RW. Endocrine basis for recurrent pregnancy loss. Obstetrics and gynecology clinics of North America 2014;41: 103-112.	PCOS – discussed in other chapter
Kumar K, Deka D, Singh A, Mitra DK, Vanitha BR, Dada R. Predictive value of DNA integrity analysis in idiopathic recurrent pregnancy loss following spontaneous conception. Journal of assisted reproduction and genetics 2012;29: 861-867.	Review of unacceptable quality
Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. Human reproduction 2004;19: 1644-1646.	Included in question 1
Leslie PW, Campbell KL, Little MA. Pregnancy loss in Nomadic and settled women in Turkana, Kenya: a prospective study. Human biology 1993;65: 237-254.	Not relevant
Madhappan B, Kempuraj D, Christodoulou S, Tsapikidis S, Boucher W, Karagiannis V, Athanassiou A, Theoharides TC. High levels of intrauterine corticotropin-releasing hormone, urocortin, tryptase, and interleukin-8 in spontaneous abortions. Endocrinology 2003;144: 2285-2290.	hypothesis generating
Marquard K, Westphal LM, Milki AA, Lathi RB. Etiology of recurrent pregnancy loss in women over the age of 35 years. Fertility and sterility 2010;94: 1473-1477.	age over 35 most miscarriages fetal cause – relevant for other chapters
Maryam K, Bouzari Z, Basirat Z, Kashifard M, Zadeh MZ. The comparison of insulin resistance frequency in patients with recurrent early pregnancy loss to normal individuals. BMC research notes 2012;5: 133.	Relevance unclear
McGregor JA, French JI, Parker R, Draper D, Patterson E, Jones W, Thorsgard K, McFee J. Prevention of premature birth by screening and treatment for common genital tract infections: results of a prospective controlled evaluation. American journal of obstetrics and gynecology 1995;173: 157-167.	screening too late to stop early miscarriage
Meeker JD, Maity A, Missmer SA, Williams PL, Mahalingaiah S, Ehrlich S, Berry KF, Altshul L, Perry MJ, Cramer DW et al. Serum concentrations of polychlorinated biphenyls in relation to in vitro fertilization outcomes. Environmental health perspectives 2011;119: 1010-1016.	PCB effect failed implantation
Metwally M, Saravelos SH, Ledger WL, Li TC. Body mass index and risk of miscarriage in women with recurrent miscarriage. Fertility and sterility 2010;94: 290-295.	Included in question 1
Metwally M, Tuckerman EM, Laird SM, Ledger WL, Li TC. Impact of high body mass index on endometrial morphology and function in the peri-implantation period in women with recurrent miscarriage. Reproductive biomedicine online 2007;14: 328-334.	More recent study of the same group included
Pandey S, Pandey S, Maheshwari A, Bhattacharya S. The impact of female obesity on the outcome of fertility treatment. Journal of human reproductive sciences 2010;3: 62-67.	Included in question 1
Perin PM, Maluf M, Czeresnia CE, Januario DA, Saldiva PH. Impact of short-term preconceptional exposure to particulate air pollution on treatment outcome in couples undergoing in vitro fertilization and embryo transfer (IVF/ET). Journal of assisted reproduction and genetics 2010;27: 371-382.	Small study
Perin PM, Maluf M, Czeresnia CE, Nicolosi Foltran Januario DA, Nascimento Saldiva PH. Effects of exposure to high levels of particulate air pollution during the follicular phase of the conception cycle on pregnancy outcome in	Small study

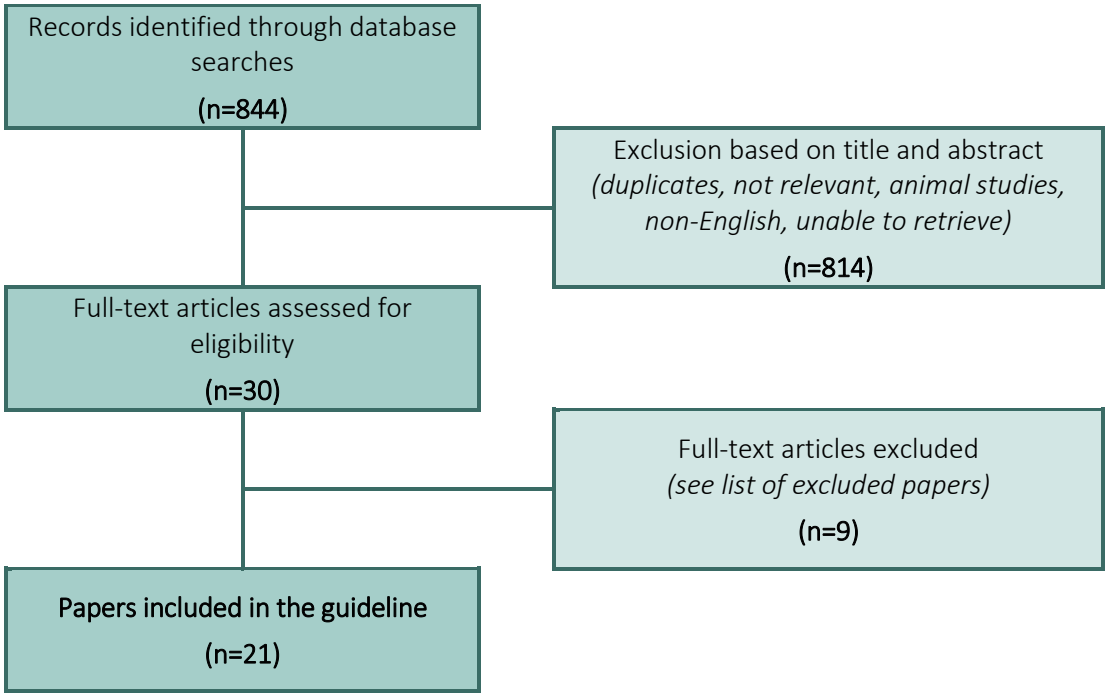
couples undergoing in vitro fertilization and embryo transfer. Fertility and sterility 2010;93: 301-303.	
Pons I, Cercas R, Villas C, Brana C, Fernandez-Shaw S. One abstinence day decreases sperm DNA fragmentation in 90 % of selected patients. Journal of assisted reproduction and genetics 2013;30: 1211-1218.	Semen quality – discussed in male factor chapter – excluded here
Ribas-Maynou J, Garcia-Peiro A, Fernandez-Encinas A, Amengual MJ, Prada E, Cortes P, Navarro J, Benet J. Double stranded sperm DNA breaks, measured by Comet assay, are associated with unexplained recurrent miscarriage in couples without a female factor. PloS one 2012;7: e44679.	Semen quality – discussed in male factor chapter – excluded here
Robinson L, Gallos ID, Conner SJ, Rajkhowa M, Miller D, Lewis S, Kirkman-Brown J, Coomarasamy A. The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Human reproduction 2012;27: 2908-2917.	Topic discussed in the male factor chapter
Rogenhofer N, Engels L, Bogdanova N, Tuttelmann F, Thaler CJ, Markoff A. Independent association of the M2/ANXA5 haplotype with recurrent pregnancy loss (RPL) in PCOS patients. Metabolism: clinical and experimental 2013;62: 1057-1060.	Not relevant to question
Rubio C, Gil-Salom M, Simon C, Vidal F, Rodrigo L, Minguez Y, Remohi J, Pellicer A. Incidence of sperm chromosomal abnormalities in a risk population: relationship with sperm quality and ICSI outcome. Human reproduction 2001;16: 2084-2092.	Semen quality – discussed in male factor chapter – excluded here
Ruixue W, Hongli Z, Zhihong Z, Rulin D, Dongfeng G, Ruizhi L. The impact of semen quality, occupational exposure to environmental factors and lifestyle on recurrent pregnancy loss. Journal of assisted reproduction and genetics 2013;30: 1513-1518.	Semen quality – discussed in male factor chapter – excluded here
Ruixue W, Hongli Z, Zhihong Z, Rulin D, Dongfeng G, Ruizhi L. The impact of semen quality, occupational exposure to environmental factors and lifestyle on recurrent pregnancy loss. Journal of assisted reproduction and genetics 2013;30: 1513-1518.	Very small study
Sagle M, Bishop K, Ridley N, Alexander FM, Michel M, Bonney RC, Beard RW, Franks S. Recurrent early miscarriage and polycystic ovaries. BMJ (Clinical research ed) 1988;297: 1027-1028.	very small poorly controlled study
Saxena P, Misro MM, Chaki SP, Chopra K, Roy S, Nandan D. Is abnormal sperm function an indicator among couples with recurrent pregnancy loss? Fertility and sterility 2008;90: 1854-1858.	Semen quality – discussed in male factor chapter – excluded here
Saxena P, Misro MM, Roy S, Chopra K, Sinha D, Nandan D, Trivedi SS. Possible role of male factors in recurrent pregnancy loss. Indian journal of physiology and pharmacology 2008;52: 274-282.	Semen quality – discussed in male factor chapter – excluded here
Sbracia S, Cozza G, Grasso JA, Mastrone M, Scarpellini F. Semen parameters and sperm morphology in men in unexplained recurrent spontaneous abortion, before and during a 3 year follow-up period. Human reproduction 1996;11: 117-120.	Semen quality – discussed in male factor chapter – excluded here
Schaumburg I, Boldsen JL. Waiting time to pregnancy and pregnancy outcome among Danish workers in the textile, clothing, and footwear industries. Scandinavian journal of social medicine 1992;20: 110-114.	compared delay in time to conception with miscarriage not exposure to toxins
Schieve LA, Cohen B, Nannini A, Ferre C, Reynolds MA, Zhang Z, Jeng G, Macaluso M, Wright VC. A population-based study of maternal and perinatal outcomes associated with assisted reproductive technology in Massachusetts. Maternal and child health journal 2007;11: 517-525.	After IVF – not RPL
Schwartz D, Mayaux MJ, Guihard-Moscato ML, Czyglik F, David G. Abortion rate in A.I.D. and semen characteristics: a study of 1345 pregnancies. Andrologia 1986;18: 292-298.	Semen quality – discussed in male factor chapter – excluded here
Shy CM. Epidemiological studies of neurotoxic, reproductive, and carcinogenic effects of complex mixtures. Environmental health perspectives 1993;101 Suppl 4: 183-186.	vague review only
Simpson JL. Incidence and timing of pregnancy losses: relevance to evaluating safety of early prenatal diagnosis. American journal of medical genetics 1990;35: 165-173.	Not relevant
Simpson JL, Gray RH, Queenan JT, Barbato M, Perez A, Mena P, Kambic RT, Pardo F, Stevenson W, Li C et al. Further evidence that infection is an infrequent cause of first trimester spontaneous abortion. Human reproduction 1996;11: 2058-2060.	only clinically diagnosed infections

Smits LJ, Nelen WL, Wouters MG, Straatman H, Jongbloet PH, Zielhuis GA. Conditions at conception in women with recurrent miscarriage. Social biology 1998;45: 143-149.	Not relevant
Stallman HM, McDermott BM, Beckmann MM, Kay Wilson M, Adam K. Women who miscarry: The effectiveness and clinical utility of the Kessler 10 questionnaire in screening for ongoing psychological distress. The Australian & New Zealand journal of obstetrics & gynaecology 2010;50: 70-76.	not relevant measuring stress in single miscarriage only
Stephenson MD. Frequency of factors associated with habitual abortion in 197 couples. Fertility and sterility 1996;66: 24-29.	only one patient
Sun L, Lv H, Wei W, Zhang D, Guan Y. Angiotensin-converting enzyme D/I and plasminogen activator inhibitor-1 4G/5G gene polymorphisms are associated with increased risk of spontaneous abortions in polycystic ovarian syndrome. Journal of endocrinological investigation 2010;33: 77-82.	Not relevant to question
Talebi AR, Vahidi S, Aflatoonian A, Ghasemi N, Ghasemzadeh J, Firoozabadi RD, Moein MR. Cytochemical evaluation of sperm chromatin and DNA integrity in couples with unexplained recurrent spontaneous abortions. Andrologia 2012;44 Suppl 1: 462-470.	Semen quality – discussed in male factor chapter – excluded here
Trkova M, Kapras J, Bobkova K, Stankova J, Mejsnarova B. Increased micronuclei frequencies in couples with reproductive failure. Reproductive toxicology (Elmsford, NY) 2000;14: 331-335.	Semen quality – discussed in male factor chapter – excluded here
Ueno S, Ezoe K, Abe T, Yabuuchi A, Uchiyama K, Okuno T, Kobayashi T, Kato K. Maternal age and initial beta-hCG levels predict pregnancy outcome after single vitrified-warmed blastocyst transfer. Journal of assisted reproduction and genetics 2014;31: 1175-1181.	no analysis miscarriage rates
van den Boogaard E, Cohn DM, Korevaar JC, Dawood F, Vissenberg R, Middeldorp S, Goddijn M, Farquharson RG. Number and sequence of preceding miscarriages and maternal age for the prediction of antiphospholipid syndrome in women with recurrent miscarriage. Fertility and sterility 2013;99: 188-192.	Not relevant
Vansenne F, Goddijn M, Redeker B, Snijder S, Gerssen-Schoorl K, Lemmink H, Leschot NJ, van der Veen F, Bossuyt PM, de Borgie CA. Knowledge and perceived risks in couples undergoing genetic testing after recurrent miscarriage or for poor semen quality. Reproductive biomedicine online 2011;23: 525-533.	about knowledge of genetic testing only
Velissariou V, Lyberatou E, Antonopoulou E, Polymilis C. Chromosome breakage in individuals with single-cell structural aberrations and habitual abortions. Gynecologic and obstetric investigation 1993;36: 71-74.	Semen quality – discussed in male factor chapter – excluded here
Venkatesh S, Thilagavathi J, Kumar K, Deka D, Talwar P, Dada R. Cytogenetic, Y chromosome microdeletion, sperm chromatin and oxidative stress analysis in male partners of couples experiencing recurrent spontaneous abortions. Archives of gynecology and obstetrics 2011;284: 1577-1584.	Semen quality – discussed in male factor chapter – excluded here
Venners SA, Wang X, Chen C, Wang L, Chen D, Guang W, Huang A, Ryan L, O'Connor J, Lasley B et al. Paternal smoking and pregnancy loss: a prospective study using a biomarker of pregnancy. American journal of epidemiology 2004;159: 993-1001.	Included in question 1
Verstraelen H, Senok AC. Vaginal lactobacilli, probiotics, and IVF. Reproductive biomedicine online 2005;11: 674-675.	not relevant
Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertility and sterility 2003;79: 577-584.	Not relevant
Windham GC, Waller K, Anderson M, Fenster L, Mendola P, Swan S. Chlorination by-products in drinking water and menstrual cycle function. Environmental health perspectives 2003;111: 935-941; discussion A409.	menstrual cycle length as outcome only not miscarriage
Zhang BY, Wei YS, Niu JM, Li Y, Miao ZL, Wang ZN. Risk factors for unexplained recurrent spontaneous abortion in a population from southern China. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2010;108: 135-138.	Included in question 1
Zhang L, Wang L, Zhang X, Xu G, Zhang W, Wang K, Wang Q, Qiu Y, Li J, Gai L. Sperm chromatin integrity may predict future fertility for unexplained recurrent spontaneous abortion patients. International journal of andrology 2012;35: 752-757.	Semen quality – discussed in male factor chapter – excluded here

Zini A. Are sperm chromatin and DNA defects relevant in the clinic? Systems biology in reproductive medicine 2011;57: 78-85.	Semen quality – discussed in male factor chapter – excluded here

3. WHAT IS THE VALUE OF MEDICAL AND FAMILY HISTORY TAKING IN ESTABLISHING THE PROGNOSIS OF RPL?

Flowchart

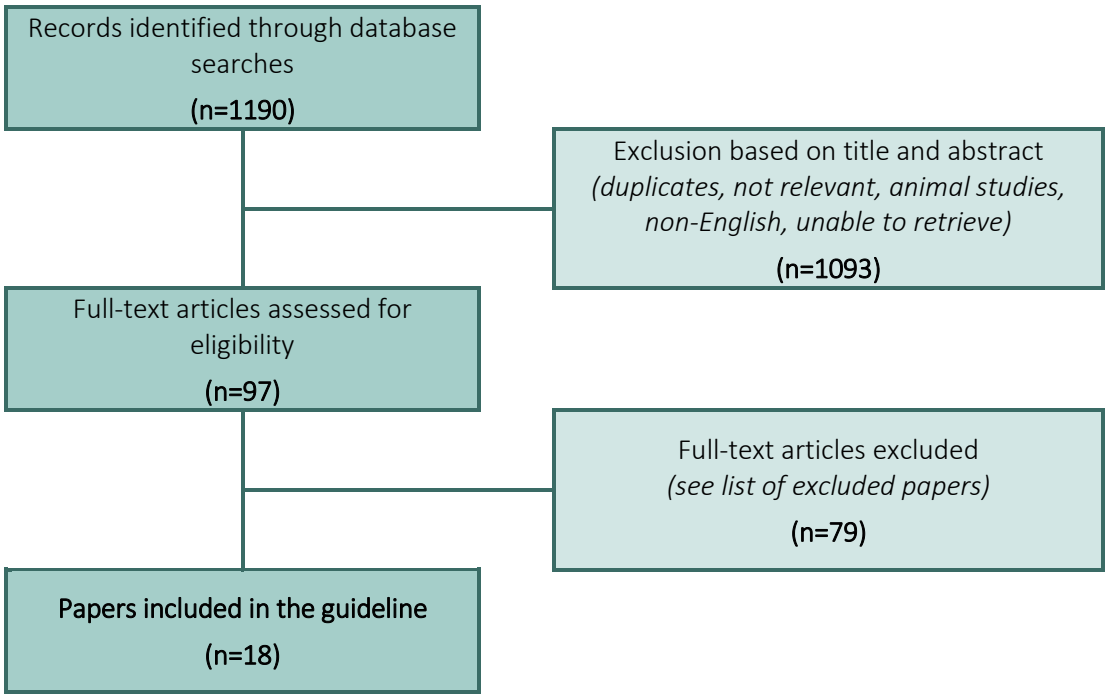


List of excluded papers

	EXCLUSION CRITERIA
Bentolila Y, Ratzon R, Shoham-Vardi I, Serjienko R, Mazor M, Bashiri A. Effect of interpregnancy interval on outcomes of pregnancy after recurrent pregnancy loss. The journal of maternal-fetal & neonatal medicine 2013;26: 1459-1464.	No information on length of follow-up, no adjustement for # PL.
Cauchi MN, Pepperell R, Kloss M, Lim D. Predictors of pregnancy success in repeated miscarriage. American journal of reproductive immunology (New York, NY : 1989) 1991;26: 72-75.	The study doesn't provide sufficient data.
Cowchock FS, Smith JB. Predictors for live birth after unexplained spontaneous abortions: correlations between immunologic test results, obstetric histories, and outcome of next pregnancy without treatment. American journal of obstetrics and gynecology 1992;167: 1208-1212.	Excluded based on low quality
Houwert-de Jong MH, Termijtelen A, Eskes TK, Mantingh A, Bruinse HW. The natural course of habitual abortion. European journal of obstetrics, gynecology, and reproductive biology 1989;33: 221-228.	Not relevant for the question
Miskovic S, Culic V, Konjevoda P, Pavelic J. Positive reproductive family history for spontaneous abortion: predictor for recurrent miscarriage in young couples. European journal of obstetrics, gynecology, and reproductive biology 2012;161: 182-186.	life time incidence of PL among relatives to per pregnancy rates of miscarriage in the general population – not relevant
Nielsen HS, Andersen AM, Kolte AM, Christiansen OB. A firstborn boy is suggestive of a strong prognostic factor in secondary recurrent miscarriage: a confirmatory study. Fertility and sterility 2008;89: 907-911.	Discussed in immunology chapter
Tulppala M, Palosuo T, Ramsay T, Miettinen A, Salonen R, Ylikorkala O. A prospective study of 63 couples with a history of recurrent spontaneous abortion: contributing factors and outcome of subsequent pregnancies. Human reproduction 1993;8: 764-770.	No relevant date
van Oppenraaij RH, Jauniaux E, Christiansen OB, Horcajadas JA, Farquharson RG, Exalto N. Predicting adverse obstetric outcome after early pregnancy events and complications: a review. Human reproduction update 2009;15: 409-421.	Not RPL specific
Vlaanderen W, Treffers PE. Prognosis of subsequent pregnancies after recurrent spontaneous abortion in first trimester. British medical journal (Clinical research ed) 1987;295: 92-93.	Unacceptable quality

4. WHAT IS THE VALUE OF SCREENING FOR GENETIC FACTORS IN THE DIAGNOSIS OF RPL?

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Abuelo DN, Barsel-Bowers G. Prognosis for couples who have experienced repeated pregnancy loss. Fertility and sterility 1983;40: 844-845.	Older study
Agrawal S, Parveen F, Faridi RM, Prakash S. Interleukin-1 gene cluster variants and recurrent pregnancy loss among North Indian women: retrospective study and meta-analysis. Reproductive biomedicine online 2012;24: 342-351.	Unacceptable quality
Aldrich CL, Stephenson MD, Karrison T, Odem RR, Branch DW, Scott JR, Schreiber JR, Ober C. HLA-G genotypes and pregnancy outcome in couples with unexplained recurrent miscarriage Molecular human reproduction. 2001, pp. 1167-1172.	HLA G alleles sharing
Al-Khateeb GM, Sater MS, Finan RR, Mustafa FE, Al-Busaidi AS, Al-Sulaiti MA, Almawi WY. Analysis of interleukin-18 promoter polymorphisms and changes in interleukin-18 serum levels underscores the involvement of interleukin-18 in recurrent spontaneous miscarriage. Fertility and sterility 2011;96: 921-926.	IL 18 polymorphisms
Andreasen L, Christiansen OB, Niemann I, Bolund L, Sunde L. NLRP7 or KHDC3L genes and the etiology of molar pregnancies and recurrent miscarriage. Molecular human reproduction 2013;19: 773-781.	Molar pregnancies
Angiolucci M, Murru R, Melis G, Carcassi C, Mais V. Association between different morphological types and abnormal karyotypes in early pregnancy loss. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2011;37: 219-225.	Not all RPL
Benzacken B, Carbillon L, Dupont C, Siffroi JP, Monier-Gavelle F, Bucourt M, Uzan M, Wolf JP. Lack of submicroscopic rearrangements involving telomeres in reproductive failures. Human reproduction 2002;17: 1154-1157.	Not relevant
Bruyere H, Rajcan-Separovic E, Doyle J, Pantzar T, Langlois S. Familial cryptic translocation (2;17) ascertained through recurrent spontaneous abortions. American journal of medical genetics Part A 2003;123a: 285-289.	Case study - 3 miscarriages and 2 neonatal deaths
Bug S, Solfrank B, Schmitz F, Pricelius J, Stecher M, Craig A, Botcherby M, Nevinny-Stickel-Hinzpeter C. Diagnostic utility of novel combined arrays for genome-wide simultaneous detection of aneuploidy and uniparental isodisomy in losses of pregnancy. Molecular cytogenetics 2014;7: 43.	compariosn testing group to heterogenous
Caramins MC, Saville T, Shakeshaft R, Mullan GL, Miller B, Yip MY, Buckley MF. A comparison of molecular and cytogenetic techniques for the diagnosis of pregnancy loss. Genetics in medicine : official journal of the American College of Medical Genetics 2011;13: 46-51.	Not all POC from RPL patients
Carp H, Feldman B, Oelsner G, Schiff E. Parental karyotype and subsequent live births in recurrent miscarriage. Fertility and sterility 2004;81: 1296-1301.	More recent studies available
Carp H, Guetta E, Dorf H, Soriano D, Barkai G, Schiff E. Embryonic karyotype in recurrent miscarriage with parental karyotypic aberrations. Fertility and sterility 2006;85: 446-450.	G banding
Carp H, Toder V, Aviram A, Daniely M, Mashiach S, Barkai G. Karyotype of the abortus in recurrent miscarriage. Fertility and sterility 2001;75: 678-682.	Included in overview Van den Berg 2012
Clark DA, Daya S, Coulam CB, Gunby J. Implication of abnormal human trophoblast karyotype for the evidence-based approach to the understanding, investigation, and treatment of recurrent spontaneous abortion. The Recurrent Miscarriage Immunotherapy Trialists Group. American journal of reproductive immunology (New York, NY : 1989) 1996;35: 495-498.	editorial

Clifford K, Rai R, Watson H, Regan L. An informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases. Human reproduction 1994;9: 1328-1332.	Inconsistencies in paper
Daniely M, Aviram-Goldring A, Barkai G, Goldman B. Detection of chromosomal aberration in fetuses arising from recurrent spontaneous abortion by comparative genomic hybridization. Human reproduction 1998;13: 805-809.	technical
De Gregori M, Ciccone R, Magini P, Pramparo T, Gimelli S, Messa J, Novara F, Vetro A, Rossi E, Maraschio P et al. Cryptic deletions are a common finding in "balanced" reciprocal and complex chromosome rearrangements: a study of 59 patients. Journal of medical genetics 2007;44: 750-762.	Technical
Fan W, Li S, Huang Z, Chen Q. Relationship between HLA-G polymorphism and susceptibility to recurrent miscarriage: a meta-analysis of non-family-based studies (Provisional abstract) Journal of assisted reproduction and genetics. 2014, pp. 173-184.	HLA- G 14 bp - but more studies needed
Finan RR, Al-Irhayim Z, Mustafa FE, Al-Zaman I, Mohammed FA, Al-Khateeb GM, Madan S, Issa AA, Almawi WY. Tumor necrosis factor-alpha polymorphisms in women with idiopathic recurrent miscarriage. Journal of reproductive immunology 2010;84: 186-192.	underpowered
Franssen MT, Korevaar JC, Tjoa WM, Leschot NJ, Bossuyt PM, Knegt AC, Suykerbuyk RF, Hochstenbach R, van der Veen F, Goddijn M. Inherited unbalanced structural chromosome abnormalities at prenatal chromosome analysis are rarely ascertained through recurrent miscarriage. Prenatal diagnosis 2008;28: 408-411.	Prenatal chromosome analysis
Fryns JP, Van Buggenhout G. Structural chromosome rearrangements in couples with recurrent fetal wastage. European journal of obstetrics, gynecology, and reproductive biology 1998;81: 171-176.	Prevalence study
Gada Saxena S, Desai K, Shewale L, Ranjan P, Saranath D. Chromosomal aberrations in 2000 couples of Indian ethnicity with reproductive failure. Reproductive biomedicine online 2012;25: 209-218.	Prevalance in India
Goddijn M, Joosten JH, Knegt AC, van derVeen F, Franssen MT, Bonsel GJ, Leschot NJ. Clinical relevance of diagnosing structural chromosome abnormalities in couples with repeated miscarriage. Human reproduction 2004;19: 1013-1017.	No offspring unbalanced
Granfors M, Karypidis H, Hosseini F, Skjoldebrand-Sparre L, Stavreus-Evers A, Bremme K, Landgren BM, Sundstrom-Poromaa I, Wikstrom AK, Akerud H. Phosphodiesterase 8B gene polymorphism in women with recurrent miscarriage: a retrospective case control study. BMC medical genetics 2012;13: 121.	Specific gene polymorphism
Hayashi Y, Sasaki H, Suzuki S, Nishiyama T, Kitaori T, Mizutani E, Suzumori N, Sugiura-Ogasawara M. Genotyping analyses for polymorphisms of ANXA5 gene in patients with recurrent pregnancy loss. Fertility and sterility 2013;100: 1018-1024.	Association between SNP5 and RM but subsequent LB rate was same with our without; Not worth testing
Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertility and sterility 2010;93: 1234-1243.	Prevalence study
Jauniaux E, Farquharson RG, Christiansen OB, Exalto N. Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. Human reproduction 2006;21: 2216-2222.	guideline
Kajii T, Ferrier A. Cytogenetics of aborters and abortuses. American journal of obstetrics and gynecology 1978;131: 33-38.	Older study
Kalousek DK. Clinical significance of morphologic and genetic examination of spontaneously aborted embryos. American journal of reproductive immunology (New York, NY : 1989) 1998;39: 108-119.	Not relevant
Kano T, Mori T, Kimura A. Gender ratio distortion in abortuses and live births from patients with recurrent spontaneous abortion. American journal of reproductive immunology (New York, NY : 1989) 2009;62: 125-127.	scientific method not described
Karvela M, Papadopoulou S, Tsaliki E, Konstantakou E, Hatzaki A, Florentin-Arar L, Lamnissou K. Endothelial nitric oxide synthase gene	Specific gene polymorphism

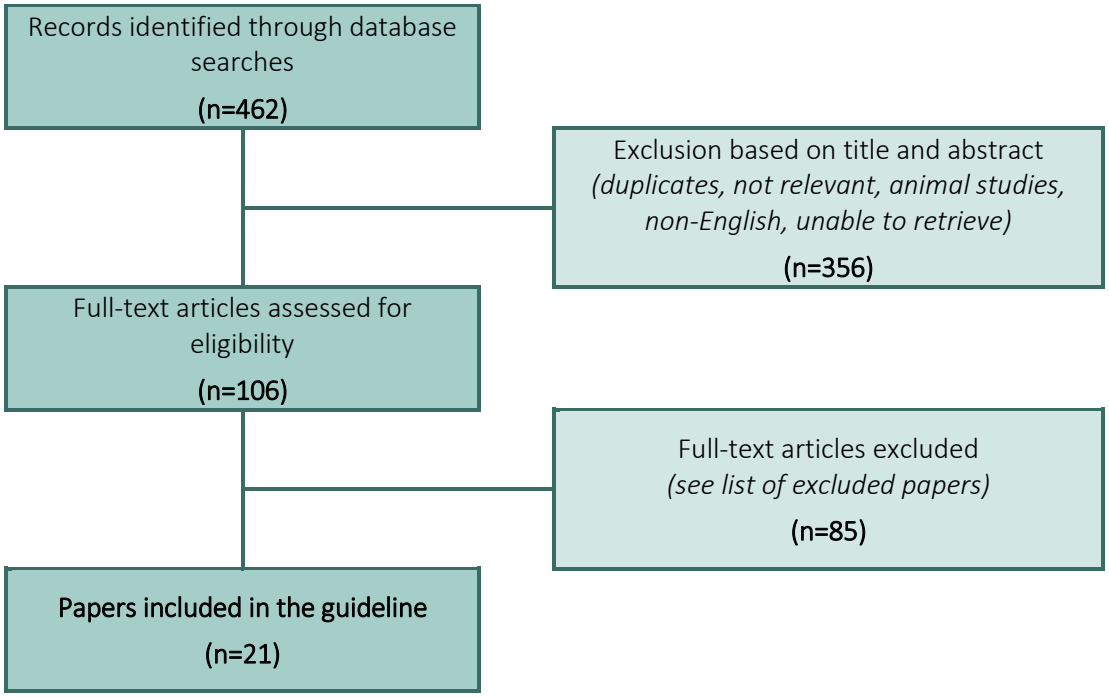
polymorphisms in recurrent spontaneous abortions. Archives of gynecology and obstetrics 2008;278: 349-352.	
Kochhar PK, Ghosh P. Reproductive outcome of couples with recurrent miscarriage and balanced chromosomal abnormalities. The journal of obstetrics and gynaecology research 2013;39: 113-120.	Prevalance in India
Kuo PL, Guo HR. Mechanism of recurrent spontaneous abortions in women with mosaicism of X-chromosome aneuploidies. Fertility and sterility 2004;82: 1594-1601.	RPL X chromosome mosaicism
Laurino MY, Bennett RL, Saraiya DS, Baumeister L, Doyle DL, Leppig K, Pettersen B, Resta R, Shields L, Uhrich S et al. Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. Journal of genetic counseling 2005;14: 165-181.	Unacceptable quality
Lee MH, Park SY, Kim YM, Kim JM, Han JY, Kim MY, Ryu HM. Prenatal diagnosis of a familial complex chromosomal rearrangement involving chromosomes 5, 10, 16 and 18. Prenatal diagnosis 2002;22: 102-104.	G banding
Liu C, Wang J, Zhou S, Wang B, Ma X. Association between -238 but not -308 polymorphism of Tumor necrosis factor alpha (TNF-alpha)v and unexplained recurrent spontaneous abortion (URSA) in Chinese population. Reproductive biology and endocrinology : RB&E 2010;8: 114.	Specific gene polymorphism
Magdoud K, Dendana M, Herbepin V, Hizem S, Ben Jazia K, Messaoudi S, Almawi WY, Touraine R, Mahjoub T. Identification of specific vascular endothelial growth factor susceptible and protective haplotypes associated with recurrent spontaneous miscarriages. Human reproduction 2012;27: 1536-1541.	Specific gene polymorphism
Marquard K, Westphal LM, Milki AA, Lathi RB. Etiology of recurrent pregnancy loss in women over the age of 35 years. Fertility and sterility 2010;94: 1473-1477.	Recommend karyotyping POC from RPL patients
Medica I, Ostojic S, Pereza N, Kastrin A, Peterlin B. Association between genetic polymorphisms in cytokine genes and recurrent miscarriage--a meta-analysis. Reproductive biomedicine online 2009;19: 406-414.	Specific gene polymorphism
Meng HX, Qi MG, Yi YY, Liu YP. Association between apolipoprotein E gene polymorphism and the risk of recurrent pregnancy loss: a meta-analysis. Journal of assisted reproduction and genetics 2013;30: 1547-1552.	Specific gene polymorphism
Messaed C, Chebaro W, Di Roberto RB, Rittore C, Cheung A, Arseneau J, Schneider A, Chen MF, Bernishke K, Surti U et al. NLRP7 in the spectrum of reproductive wastage: rare non-synonymous variants confer genetic susceptibility to recurrent reproductive wastage. Journal of medical genetics 2011;48: 540-548.	Molar pregnancies
Messaoudi S, Dandana M, Magdoud K, Meddeb S, Ben Slama N, Hizem S, Mahjoub T. Interleukin-18 promoter polymorphisms and risk of idiopathic recurrent pregnancy loss in a Tunisian population. Journal of reproductive immunology 2012;93: 109-113.	Specific gene polymorphism
Meza-Espinoza JP, Anguiano LO, Rivera H. Chromosomal abnormalities in couples with reproductive disorders. Gynecologic and obstetric investigation 2008;66: 237-240.	Prevalance in Mexico
Miskovic S, Culic V, Konjevoda P, Pavelic J. Positive reproductive family history for spontaneous abortion: predictor for recurrent miscarriage in young couples. European journal of obstetrics, gynecology, and reproductive biology 2012;161: 182-186.	No conclusion
Morikawa M, Yamada H, Kato EH, Shimada S, Yamada T, Minakami H. Embryo loss pattern is predominant in miscarriages with normal chromosome karyotype among women with repeated miscarriage. Human reproduction 2004;19: 2644-2647.	No maternal contamination testing
Nair RR, Khanna A, Singh K. Association of interleukin 1 receptor antagonist (IL1RN) gene polymorphism with recurrent pregnancy loss risk in the North Indian Population and a meta-analysis. Molecular biology reports 2014;41: 5719-5727.	Specific gene polymorphism
Nayak S, Pavone ME, Milad M, Kazer R. Aneuploidy rates in failed pregnancies following assisted reproductive technology. Journal of women's health (2002) 2011;20: 1239-1243.	Not RPL

Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in relation to the number of previous miscarriages. Fertility and sterility 2000;73: 300-304.	Included in overview Van den Berg 2012
Palmirotta R, La Farina F, Ferroni P, Ludovici G, Nigro C, Savonarola A, Raparelli V, Riondino S, Rampini MR, Guadagni F et al. TNFA gene promoter polymorphisms and susceptibility to recurrent pregnancy loss in Italian women. Reproductive sciences (Thousand Oaks, Calif) 2010;17: 659-666.	Specific gene polymorphism
Parveen F, Shukla A, Agarwal S. Cytokine gene polymorphisms in northern Indian women with recurrent miscarriages. Fertility and sterility 2013;99: 433-440.	Specific gene polymorphism
Roos A, von Kaisenberg CS, Eggermann T, Schwanitz G, Loffler C, Weise A, Mrasek K, Junge A, Caliebe A, Belitz B et al. Analysis of SYCP3 encoding synaptonemal complex protein 3 in human aneuploidies. Archives of gynecology and obstetrics 2013;288: 1153-1158.	Specific gene polymorphism
Rubio C, Simon C, Vidal F, Rodrigo L, Pehlivan T, Remohi J, Pellicer A. Chromosomal abnormalities and embryo development in recurrent miscarriage couples. Human reproduction 2003;18: 182-188.	Prevalence aneuploidy
Rull K, Christiansen OB, Nagirnaja L, Steffensen R, Margus T, Laan M. A modest but significant effect of CGB5 gene promoter polymorphisms in modulating the risk of recurrent miscarriage. Fertility and sterility 2013;99: 1930-1936.e1936.	Specific gene polymorphism
Sider D, Wilson WG, Sudduth K, Atkin JF, Kelly TE. Cytogenetic studies in couples with recurrent pregnancy loss. Southern medical journal 1988;81: 1521-1524.	Older study
Smith A, Gaha TJ. Data on families of chromosome translocation carriers ascertained because of habitual spontaneous abortion. The Australian & New Zealand journal of obstetrics & gynaecology 1990;30: 57-62.	Older study
Steck T, Giess R, Suetterlin MW, Bolland M, Wiest S, Poehls UG, Dietl J. Leukaemia inhibitory factor (LIF) gene mutations in women with unexplained infertility and recurrent failure of implantation after IVF and embryo transfer. European journal of obstetrics, gynecology, and reproductive biology 2004;112: 69-73.	RIF after IVF - not RPL
Stephenson MD, Awartani KA, Robinson WP. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case-control study. Human reproduction 2002;17: 446-451.	Included in overview Van den Berg 2012
Stern JJ, Dorfmann AD, Gutierrez-Najar AJ, Cerrillo M, Coulam CB. Frequency of abnormal karyotypes among abortuses from women with and without a history of recurrent spontaneous abortion. Fertility and sterility 1996;65: 250-253.	Included in overview Van den Berg 2012
Su MT, Lin SH, Chen YC, Kuo PL. Genetic association studies of ACE and PAI-1 genes in women with recurrent pregnancy loss: a systematic review and meta-analysis (Provisional abstract) Thrombosis and haemostasis. 2013, pp. 8-15.	Specific gene polymorphism
Sugiura-Ogasawara M. Reciprocal translocation carriers in recurrent miscarriage parents may yield an unbalanced fetal chromosome pattern. Human reproduction 2004;19: 2171-2172; author reply 2172.	G banding
Sugiura-Ogasawara M, Ozaki Y, Kitaori T, Kumagai K, Suzuki S. Midline uterine defect size is correlated with miscarriage of euploid embryos in recurrent cases. Fertility and sterility 2010;93: 1983-1988.	G banding
Sullivan AE, Silver RM, LaCoursiere DY, Porter TF, Branch DW. Recurrent fetal aneuploidy and recurrent miscarriage. Obstetrics and gynecology 2004;104: 784-788.	Included in overview Van den Berg 2012
Takakuwa K, Asano K, Arakawa M, Yasuda M, Hasegawa I, Tanaka K. Chromosome analysis of aborted conceptuses of recurrent aborters positive for anticardiolipin antibody. Fertility and sterility 1997;68: 54-58.	G banding
Trkova M, Kapras J, Bobkova K, Stankova J, Mejsnarova B. Increased micronuclei frequencies in couples with reproductive failure. Reproductive toxicology (Elmsford, NY) 2000;14: 331-335.	Increase micronucleus instability inf and RPL
Tunc E, Demirhan O, Demir C, Tastemir D. Cytogenetic study of recurrent miscarriages and their parents. Genetika 2007;43: 545-552.	G banding

Vaiman D. Genetic regulation of recurrent spontaneous abortion in humans. Biomedical journal 2014.	Opinion paper
van den Boogaard E, Hermens RP, Verhoeve HR, Kremer JA, van der Veen F, Knegt AC, Goddijn M. Selective karyotyping in recurrent miscarriage: are recommended guidelines adopted in daily clinical practice? Human reproduction 2011;26: 1965-1970.	Selective karyotyping
van Leeuwen M, Vansenne F, Korevaar JC, van der Veen F, Goddijn M, Mol BW. Economic analysis of chromosome testing in couples with recurrent miscarriage to prevent handicapped offspring. Human reproduction 2013;28: 1737-1742.	Economic analysis
Vansenne F, de Borgie CA, Korevaar JC, Franssen MT, Pajkrt E, Hansson KB, Leschot NJ, Bossuyt PM, van der Veen F, Goddijn M. Low uptake of prenatal diagnosis after established carrier status of a balanced structural chromosome abnormality in couples with recurrent miscarriage. Fertility and sterility 2010;94: 296-300.e291-293.	Not relevant PND established pregnancy
Wang JY, Zhen DK, Zilberstein ME, Falco VM, Bianchi DW. Non-invasive exclusion of fetal aneuploidy in an at-risk couple with a balanced translocation. Molecular human reproduction 2000;6: 103-106.	Technical
Wang X, Jiang W, Zhang D. Association of 14-bp insertion/deletion polymorphism of HLA-G gene with unexplained recurrent spontaneous abortion: A meta-analysis Tissue antigens. 2013, pp. 108-115.	Specific gene polymorphism
Wang X, Li B, Wang J, Lei J, Liu C, Ma Y, Zhao H. Evidence that miR-133a causes recurrent spontaneous abortion by reducing HLA-G expression. Reproductive biomedicine online 2012;25: 415-424.	miRNA expression
Wang Z, Wang P, Wang X, He X, Wang Z, Xu D, Hu J, Wang B. Significant association between angiotensin-converting enzyme gene insertion/deletion polymorphism and risk of recurrent miscarriage: a systematic review and meta-analysis (Provisional abstract) Metabolism: clinical and experimental. 2013, pp. epub.	Specific gene polymorphism
Waters JJ, Campbell PL, Crocker AJ, Campbell CM. Phenotypic effects of balanced X-autosome translocations in females: a retrospective survey of 104 cases reported from UK laboratories. Human genetics 2001;108: 318-327.	Unable to ascertain RM link as group not separated out.
Yang C, Fangfang W, Jie L, Yanlong Y, Jie W, Xuefei L, Xuerong Z, Yanling H. Angiotensin-converting enzyme insertion/deletion (I/D) polymorphisms and recurrent pregnancy loss: a meta-analysis (Provisional abstract) Journal of assisted reproduction and genetics. 2012, pp. 1167-1173.	Specific gene polymorphism
Yuce H, Tekedereli I, Elyas H. Cytogenetic results of recurrent spontaneous abortions in Turkey. Medical science monitor : international medical journal of experimental and clinical research 2007;13: Cr286-289.	Prevalence study in Turkey
Zammiti W, Mtiraoui N, Cochery-Nouvellon E, Mahjoub T, Almawi WY, Gris JC. Association of -592C/A, -819C/T and -1082A/G interleukin-10 promoter polymorphisms with idiopathic recurrent spontaneous abortion. Molecular human reproduction 2006;12: 771-776.	Specific gene polymorphism
Zammiti W, Mtiraoui N, Khairi H, Gris JC, Almawi WY, Mahjoub T. Associations between tumor necrosis factor-alpha and lymphotoxin-alpha polymorphisms and idiopathic recurrent miscarriage. Reproduction (Cambridge, England) 2008;135: 397-403.	Specific gene polymorphism
Zhang B, Liu T, Wang Z. Association of tumor necrosis factor-alpha gene promoter polymorphisms (-308G/A, -238G/A) with recurrent spontaneous abortion: a meta-analysis. Human immunology 2012;73: 574-579.	Specific gene polymorphism

5. What is the value of thrombophilia screening in the diagnosis of RPL? (including aim and indications)

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Abraitis V, Simoliuniene R, Mongirdiene A, Makari S. Prevalence of activated protein C resistance among women with recurrent miscarriage. Medicina 2004;40: 225-231.	Similar data available from reviews
Adams M. Measurement of lupus anticoagulants: an update on quality in laboratory testing. Seminars in thrombosis and hemostasis 2013;39: 267-271.	Non-systematic review
Aksoy M, Tek I, Karabulut H, Berker B, Soylemez F. The role of thrombofilia related to Factor V Leiden and Factor II G20210A mutations in recurrent abortions. J Pak Med Assoc 2005;55: 104-108.	Excluded in review Bradley 2012: reported consanguinity in cases
Al Samarrai AA, Hilmi FA, Al-Allawi NA, Murad AF. Antiphospholipid antibodies in iraqi women with recurrent mid-trimester abortions. Journal of laboratory physicians 2012;4: 78-82.	Similar data available from reviews
Alarcon-Segovia D. The antiphospholipid story. The Journal of rheumatology 2003;30: 1893-1896.	editorial
Ayyub M, Khan MN, Anwar M, Waqar A, Ali W, Hussain T, Luqman M, Sultana N, Karamat KA, Saif MW. Clinicopathological features of lupus anticoagulant; experience at AFIP during last seven years. Medical science monitor : international medical journal of experimental and clinical research 2005;11: Cr536-539.	Not RPL
Bajaj PS, Veenstra DL. A risk-benefit analysis of factor V Leiden testing to improve pregnancy outcomes: a case study of the capabilities of decision modeling in genomics. Genetics in medicine : official journal of the American College of Medical Genetics 2013;15: 374-381.	Not relevant
Balasch J. Antiphospholipid antibodies: a major advance in the management of recurrent abortion. Autoimmunity reviews 2004;3: 228-233.	Non-systematic review
Bao SH, Wang XP, Lin QD, Di W, Xu L, Ding CW. The investigation on the value of repeat and combination test of ACA and anti-beta2-GPI antibody in women with recurrent spontaneous abortion. American journal of reproductive immunology (New York, NY : 1989) 2008;60: 372-378.	Similar data available from reviews
Behjati R, Modarressi MH, Jeddi-Tehrani M, Dokoohaki P, Ghasemi J, Zarnani AH, Aarabi M, Memariani T, Ghaffari M, Akhondi MA. Thrombophilic mutations in Iranian patients with infertility and recurrent spontaneous abortion. Annals of hematology 2006;85: 268-271.	Included in review Gao 2015
Bogdanova N, Markoff A. Hereditary thrombophilic risk factors for recurrent pregnancy loss. Journal of community genetics 2010;1: 47-53.	Non-systematic review
Branch DW, Gibson M, Silver RM. Clinical practice. Recurrent miscarriage. The New England journal of medicine 2010;363: 1740-1747.	Case report
Brenner B. Thrombophilia and pregnancy loss in first intended pregnancy. Journal of thrombosis and haemostasis : JTH 2005;3: 2176-2177.	commentary
Bricker L, Farquharson RG. Types of pregnancy loss in recurrent miscarriage: implications for research and clinical practice. Human reproduction 2002;17: 1345-1350.	Not relevant
Cervera R, Balasch J. Bidirectional effects on autoimmunity and reproduction. Human reproduction update 2008;14: 359-366.	Not relevant
Chakraborty P, Goswami SK, Rajani S, Sharma S, Kabir SN, Chakravarty B, Jana K. Recurrent pregnancy loss in polycystic ovary syndrome: role of hyperhomocysteinemia and insulin resistance. PloS one 2013;8: e64446.	More relevant for PCOS
Chen H, Nie S, Lu M. Association between plasminogen activator inhibitor-1 gene polymorphisms and recurrent pregnancy loss: a systematic review and meta-analysis. American journal of reproductive immunology 2015;73: 292-300.	PAI I gene polymorphism
Chen Q, Stone PR, Woon ST, Ching LM, Hung S, McCowan LM, Chamley LW. Antiphospholipid antibodies bind to activated but not resting	Basic science

endothelial cells: is an independent triggering event required to induce antiphospholipid antibody-mediated disease? Thrombosis research. 2004, pp. 101-111.	
Ciacci C, Tortora R, Scudiero O, Di Fiore R, Salvatore F, Castaldo G. Early pregnancy loss in celiac women: The role of genetic markers of thrombophilia. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2009;41: 717-720.	Celiac disease
Clark CA, Davidovits J, Spitzer KA, Laskin CA. The lupus anticoagulant: results from 2257 patients attending a high-risk pregnancy clinic. Blood 2013;122: 341-347; quiz 466.	Not RPL
de Moerloose P, Casini A, Neerman-Arbez M. Congenital fibrinogen disorders: an update. Seminars in thrombosis and hemostasis 2013;39: 585-595.	Non-systematic review
Diejomaoh MF, Al-Azemi MM, Bandar A, Egbase PE, Jirous J, Al-Othman S, Bukhadour N, Al-Sweih N. A favorable outcome of pregnancies in women with primary and secondary recurrent pregnancy loss associated with antiphospholipid syndrome. Archives of gynecology and obstetrics 2002;266: 61-66.	Treatment/prognosis
Drakeley AJ, Quenby S, Farquharson RG. Mid-trimester loss--appraisal of a screening protocol. Human reproduction 1998;13: 1975-1980.	Not relevant
Emmi G, Silvestri E, Squatrito D, Ciucciarelli L, Cameli AM, Denas G, D'Elios MM, Pengo V, Emmi L, Prisco D. An approach to differential diagnosis of antiphospholipid antibody syndrome and related conditions. TheScientificWorldJournal 2014;2014: 341342.	Not specific for RPL
Espana F, Villa P, Mira Y, Grancha S, Royo M, Estelles A, Vaya A, Aznar J. Factor V Leiden and antibodies against phospholipids and protein S in a young woman with recurrent thromboses and abortion. Haematologica 1999;84: 80-84.	Case report
Farahmand K, Totonchi M, Hashemi M, Reyhani Sabet F, Kalantari H, Gourabi H, Mohseni Meybodi A. Thrombophilic genes alterations as risk factor for recurrent pregnancy loss. The journal of maternal-fetal & neonatal medicine 2016;29: 1269-1273.	Similar data available in reviews
Ferroni P, La Farina F, Palmirotta R, Martini F, Raparelli V, Nigro C, Riondino S, Rampini MR, Basili S, Guadagni F. Predictive value of thrombopath determination in women with infertility and pregnancy complications. Clinica chimica acta 2010;411: 37-42.	Not RPL only
Franklin RD, Hollier N, Kutteh WH. beta2-Glycoprotein 1 as a marker of antiphospholipid syndrome in women with recurrent pregnancy loss. Fertility and sterility 2000;73: 531-535.	Correlation between β2-GP1-Ab and antiphospholipid Ab
Galli M, Barbui T. Antiphospholipid syndrome: definition and treatment. Seminars in thrombosis and hemostasis 2003;29: 195-204.	Non-systematic review
Glueck CJ, Wang P, Bornovali S, Goldenberg N, Sieve L. Polycystic ovary syndrome, the G1691A factor V Leiden mutation, and plasminogen activator inhibitor activity: associations with recurrent pregnancy loss. Metabolism: clinical and experimental 2003;52: 1627-1632.	PCOS rather than thrombophilia
Grandone E, Colaizzo D, Lo Bue A, Cappucci F, Cittadini E, Margaglione M. Clinical relevance of inherited thrombophilia in implantation failure: who needs to be screened? Haematologica 2003;88: Elt35.	Letter
Hillis CM, Schimmer AD, Couban S, Crowther MA. The Canadian Choosing Wisely campaign: the Canadian Hematology Society's top five tests and treatments. Annals of hematology 2015;94: 541-545.	Committee opinion
Hossain N, Shamsi T, Khan N, Naz A. Thrombophilia investigation in Pakistani women with recurrent pregnancy loss. The journal of obstetrics and gynaecology research 2013;39: 121-125.	Similar data available in reviews
Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertility and sterility 2010;93: 1234-1243.	Similar data available in reviews
Jeschke U, Toth B, Rogenhofer N, Scholz C, Wurfel W, Thaler CJ, Makrigiannakis A. Recurrent miscarriage: current concepts in diagnosis and treatment. Journal of reproductive immunology 2010;85: 25-32.	Non-systematic review

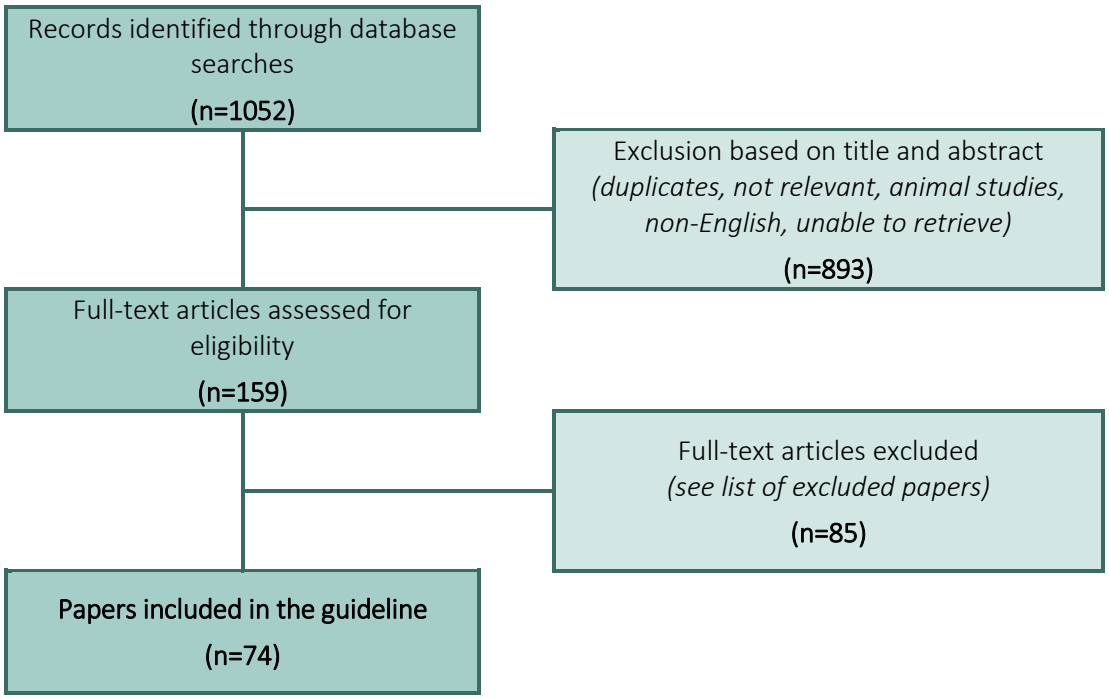
Krause M, Sonntag B, Klamroth R, Heinecke A, Scholz C, Langer C, Scharrer I, Greb RR, von Eckardstein A, Nowak-Gottl U. Lipoprotein (a) and other prothrombotic risk factors in Caucasian women with unexplained recurrent miscarriage. Results of a multicentre case-control study. Thrombosis and haemostasis 2005;93: 867-871.	Included in review Bradley 2012 and Gao 2015
Martinelli I, Battaglioli T, Mannucci PM. Screening of thrombophilia in women with failure of embryo implantation: far from being recommended. Haematologica 2003;88: Elt36.	Letter
Martinez-Zamora MA, Tassies D, Creus M, Reverter JC, Puerto B, Monteagudo J, Carmona F, Balasch J. Higher levels of procoagulant microparticles in women with recurrent miscarriage are not associated with antiphospholipid antibodies. Human reproduction 2016;31: 46-52.	Not relevant
Mercier E, Quere I, Mares P, Gris JC. Primary recurrent miscarriages: anti-beta2-glycoprotein I IgG antibodies induce an acquired activated protein C resistance that can be detected by the modified activated protein C resistance test. Blood 1998;92: 2993-2994.	Technical aspects
Middeldorp S. Is thrombophilia testing useful? Hematology 2011;2011: 150-155.	Non-systematic review
Middeldorp S. Thrombosis in women: what are the knowledge gaps in 2013? Journal of thrombosis and haemostasis : JTH 2013;11 Suppl 1: 180-191.	Non-systematic review
Mitic G, Kovac M, Povazan L, Magic Z, Djordjevic V, Salatic I, Mitic I, Novakov-Mikic A. Inherited thrombophilia is associated with pregnancy losses that occur after 12th gestational week in Serbian population. Clinical and applied thrombosis/hemostasis 2010;16: 435-439.	Included in review Bradley 2012
Mohamed MA, El Moaty MA, El Kholy AF, Mohamed SA, Ali AI. Thrombophilic gene mutations in women with repeated spontaneous miscarriage. Genetic testing and molecular biomarkers 2010;14: 593-597.	Included in review Bradley 2012 and Gao 2015
Moini A, Tadayon S, Tehranian A, Yeganeh LM, Akhoond MR, Yazdi RS. Association of thrombophilia and polycystic ovarian syndrome in women with history of recurrent pregnancy loss. Gynecological endocrinology 2012;28: 590-593.	Focused on association between thrombophilia and PCOS
Mumusoglu S, Beksac MS, Ekiz A, Ozdemir P, Hascelik G. Does the presence of autoantibodies without autoimmune diseases and hereditary thrombophilia have an effect on recurrent pregnancy loss? The journal of maternal-fetal & neonatal medicine 2015: 1-6.	Not relevant
Munakata Y, Saito T, Matsuda K, Seino J, Shibata S, Sasaki T. Detection of complement-fixing antiphospholipid antibodies in association with thrombosis. Thrombosis and haemostasis 2000;83: 728-731.	Not RPL
Myers B, Gould J. The place of beta 2 glycoprotein 1 in the assessment of antiphospholipid syndrome. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis 2003;14: 1-2.	Only subgroup had RPL
Nayfe R, Uthman I, Aoun J, Saad Aldin E, Merashli M, Khamashta MA. Seronegative antiphospholipid syndrome. Rheumatology 2013;52: 1358-1367.	RPL not discussed
Norrie G, Farquharson RG, Greaves M. Screening and treatment for heritable thrombophilia in pregnancy failure: inconsistencies among UK early pregnancy units. British journal of haematology 2009;144: 241-244.	Clinical practice
Ocak Z, Ozlu T, Ozyurt O. Association of recurrent pregnancy loss with chromosomal abnormalities and hereditary thrombophilias. African health sciences 2013;13: 447-452.	Similar data available in reviews
Ogasawara MS, Aoki K, Katano K, Ozaki Y, Suzumori K. Factor XII but not protein C, protein S, antithrombin III, or factor XIII is a predictor of recurrent miscarriage. Fertility and sterility 2001;75: 916-919.	Similar data available in reviews
Oshiro BT, Silver RM, Scott JR, Yu H, Branch DW. Antiphospholipid antibodies and fetal death. Obstetrics and gynecology 1996;87: 489-493.	Not relevant
Palomo I, Segovia F, Ortega C, Pierangeli S. Antiphospholipid syndrome: a comprehensive review of a complex and multisystemic disease. Clinical and experimental rheumatology 2009;27: 668-677.	Non-systematic review
Pantham P, Abrahams VM, Chamley LW. Role of antiphospholipid antibodies in autoimmune reproductive failure. Reproduction 2016.	Not RPL

Pasquier E, Bardin N, De Saint Martin L, Le Martelot MT, Bohec C, Roche S, Mottier D, Dignat-George F. The first assessment of soluble CD146 in women with unexplained pregnancy loss. A new insight? Thrombosis and haemostasis 2005;94: 1280-1284.	Not relevant: Soluble CD146 plasma levels
Pengo V, Ruffatti A. Laboratory diagnosis of antiphospholipid syndrome. Reumatismo 2007;59: 187-191.	editorial
Pierangeli SS, Harris EN. A quarter of a century in anticardiolipin antibody testing and attempted standardization has led us to here, which is? Seminars in thrombosis and hemostasis 2008;34: 313-328.	Non-systematic review
Quenby S, Farquharson RG, Dawood F, Hughes AM, Topping J. Recurrent miscarriage and long-term thrombosis risk: a case-control study. Human reproduction 2005;20: 1729-1732.	Incidence of thrombosis in RPL
Rai R, Tuddenham E, Backos M, Jivraj S, El'Gaddal S, Choy S, Cork B, Regan L. Thromboelastography, whole-blood haemostasis and recurrent miscarriage. Human reproduction 2003;18: 2540-2543.	Not relevant : Thromboelastography
Rai RS, Regan L, Clifford K, Pickering W, Dave M, Mackie I, McNally T, Cohen H. Antiphospholipid antibodies and beta 2-glycoprotein-I in 500 women with recurrent miscarriage: results of a comprehensive screening approach. Human reproduction 1995;10: 2001-2005.	Similar results available from reviews
Rawat A, Sikka M, Rusia U, Guleria K. Lupus anticoagulants and anticardiolipin antibodies in Indian women with spontaneous, recurrent fetal loss. Indian journal of hematology & blood transfusion 2015;31: 281-285.	Not RPL only
Reber G, de Moerloose P. Anti-beta2-glycoprotein I antibodies--when and how should they be measured? Thrombosis research 2004;114: 527-531.	Non-systematic review
Rogenhofer N, Engels L, Bogdanova N, Tuttelmann F, Thaler CJ, Markoff A. Independent association of the M2/ANXA5 haplotype with recurrent pregnancy loss (RPL) in PCOS patients. Metabolism: clinical and experimental 2013;62: 1057-1060.	Not relevant: M2 haplotype of ANXA5 gene
Ruffatti A, Tonello M, Del Ross T, Cavazzana A, Grava C, Noventa F, Tona F, Iliceto S, Pengo V. Antibody profile and clinical course in primary antiphospholipid syndrome with pregnancy morbidity. Thrombosis and haemostasis 2006;96: 337-341.	Not RPL
Sahin H, Akpak YK, Berber U, Gun I, Demirel D, Ergur AR. Expression of P-cadherin (cadherin-3) and E-selectin in the villous trophoblast of first trimester human placenta. Journal of the Turkish German Gynecological Association 2014;15: 13-17.	Not RPL
Sebire NJ, Backos M, El Gaddal S, Goldin RD, Regan L. Placental pathology, antiphospholipid antibodies, and pregnancy outcome in recurrent miscarriage patients. Obstetrics and gynecology 2003;101: 258-263.	Placental pathological examination
Sehirali S, Inal MM, Yildirim Y, Balim Z, Kosova B, Karamizrak T, Sanci M, Topcuoglu N, Tinar S. Prothrombin G20210A mutation in cases with recurrent miscarriage: a study of the mediterranean population. Archives of gynecology and obstetrics 2005;273: 170-173.	Included in review Gao 2015
Shovman O, Gilburd B, Barzilai O, Langevitz P, Shoenfeld Y. Novel insights into associations of antibodies against cardiolipin and beta2-glycoprotein I with clinical features of antiphospholipid syndrome. Clinical reviews in allergy & immunology 2007;32: 145-152.	Non-systematic review
Simcox LE, Ormesher L, Tower C, Greer IA. Thrombophilia and Pregnancy Complications. International journal of molecular sciences 2015;16: 28418-28428.	Not RPL
Skeith L, Carrier M, Kaaja R, Martinelli I, Petroff D, Schleussner E, Laskin CA, Rodger MA. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. Blood 2016.	treatment
Soare AM, Popa C. Deficiencies of proteins C, S and antithrombin and activated protein C resistance--their involvement in the occurrence of Arterial thromboses. Journal of medicine and life 2010;3: 412-415.	Not RPL

Soldo V, Cutura N, Zamurovic M. Defect of methylenetetrahydrofolate reductase in a patient with ten habitual misscarriages: a case report. Clinical and experimental obstetrics & gynecology 2012;39: 556-558.	Case report
Steegers-Theunissen RP, Van Iersel CA, Peer PG, Nelen WL, Steegers EA. Hyperhomocysteinemia, pregnancy complications, and the timing of investigation. Obstetrics and gynecology 2004;104: 336-343.	Not RPL
Stevens SM, Woller SC, Bauer KA, Kasthuri R, Cushman M, Streiff M, Lim W, Douketis JD. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. Journal of thrombosis and thrombolysis 2016;41: 154-164.	Guideline
Su MT, Lin SH, Chen YC, Kuo PL. Genetic association studies of ACE and PAI-1 genes in women with recurrent pregnancy loss: a systematic review and meta-analysis (Provisional abstract) Thrombosis and haemostasis. 2013, pp. 8-15.	PAI I gene polymorphism
Sugiura-Ogasawara M, Ozaki Y, Nakanishi T, Sato T, Suzumori N, Kumagai K. Occasional antiphospholipid antibody positive patients with recurrent pregnancy loss also merit aspirin therapy: a retrospective cohort-control study. American journal of reproductive immunology 2008;59: 235-241.	Intervention study
Tincani A, Bazzani C, Zingarelli S, Lojacono A. Lupus and the antiphospholipid syndrome in pregnancy and obstetrics: clinical characteristics, diagnosis, pathogenesis, and treatment. Seminars in thrombosis and hemostasis 2008;34: 267-273.	Non-systematic review
Toth B, Vocke F, Rogenhofer N, Friese K, Thaler CJ, Lohse P. Paternal thrombophilic gene mutations are not associated with recurrent miscarriage. American journal of reproductive immunology (New York, NY : 1989) 2008;60: 325-332.	Included in review Bradley 2012 and Gao 2015
Unfried G, Griesmacher A, Weismüller W, Nagele F, Huber JC, Tempfer CB. The C677T polymorphism of the methylenetetrahydrofolate reductase gene and idiopathic recurrent miscarriage Obstetrics and gynecology. 2002, pp. 614-619.	Similar results available from reviews
Wang X, Ma Z, Lin Q. Inherited thrombophilia in recurrent spontaneous abortion among Chinese women. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2006;92: 264-265.	Included in review Chen 2016
Woodham PC, Boggess KA, Gardner MO, Doyle NM. Routine antenatal thrombophilia screening in high-risk pregnancies: a decision analysis. American journal of perinatology 2011;28: 495-500.	Not RPL
Yamada H, Kato EH, Ebina Y, Kishida T, Hoshi N, Kobashi G, Sakuragi N, Fujimoto S. Factor XII deficiency in women with recurrent miscarriage. Gynecologic and obstetric investigation 2000;49: 80-83.	Not relevant : FXII deficiency
Yilmaz M, Delibas IB, Isaoglu U, Ingec M, Borekci B, Ulug P. Relationship between mean platelet volume and recurrent miscarriage: a preliminary study. Archives of medical science : AMS 2015;11: 989-993.	Not relevant; mean platelet volume
Younis JS, Brenner B, Ohel G, Tal J, Lanir N, Ben-Ami M. Activated protein C resistance and factor V Leiden mutation can be associated with first-as well as second-trimester recurrent pregnancy loss. American journal of reproductive immunology 2000;43: 31-35.	Included in review Bradley 2012 and Rey 2003
Yusoff NM, Abdullah WZ, Ghazali S, Othman MS, Baba AA, Abdullah N, Isa MN, Chong CL. The absence of factor V Leiden mutation in Malays with recurrent spontaneous abortions. The Australian & New Zealand journal of obstetrics & gynaecology 2002;42: 164-166.	Excluded in Bradley 2012 due to inability to compute ORs

6. What is the value of immunological screening in the diagnosis of RPL?

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Aldrich CL, Stephenson MD, Karrison T, Odem RR, Branch DW, Scott JR, Schreiber JR, Ober C. HLA-G genotypes and pregnancy outcome in couples with unexplained recurrent miscarriage. Molecular human reproduction 2001;7: 1167-1172.	No adjustment for multiple comparisons
Al-Khateeb GM, Sater MS, Finan RR, Mustafa FE, Al-Busaidi AS, Al-Sulaiti MA, Almawi WY. Analysis of interleukin-18 promoter polymorphisms and changes in interleukin-18 serum levels underscores the involvement of interleukin-18 in recurrent spontaneous miscarriage. Fertility and sterility 2011;96: 921-926.	IL18 gene
Aruna M, Sirisha PV, Andal Bhaskar S, Tarakeswari S, Thangaraj K, Reddy BM. Role of 14-bp insertion/deletion polymorphism in HLA-G among Indian women with recurrent spontaneous abortions. Tissue antigens 2011;77: 131-135.	Patients and controls ethnically heterogeneous
Bahar AM, Kwak JY, Beer AE, Kim JH, Nelson LA, Beaman KD, Gilman-Sachs A. Antibodies to phospholipids and nuclear antigens in non-pregnant women with unexplained spontaneous recurrent abortions. Journal of reproductive immunology 1993;24: 213-222.	Small study
Bellver J, Soares SR, Alvarez C, Munoz E, Ramirez A, Rubio C, Serra V, Remohi J, Pellicer A. The role of thrombophilia and thyroid autoimmunity in unexplained infertility, implantation failure and recurrent spontaneous abortion. Human reproduction 2008;23: 278-284.	TPO
Bizzaro N, Tonutti E, Villalta D, Tampoia M, Tozzoli R. Prevalence and clinical correlation of anti-phospholipid-binding protein antibodies in anticardiolipin-negative patients with systemic lupus erythematosus and women with unexplained recurrent miscarriages. Archives of pathology & laboratory medicine 2005;129: 61-68.	Males and older individuals among controls
Bussen S, Steck T. Thyroid autoantibodies in euthyroid non-pregnant women with recurrent spontaneous abortions. Human reproduction 1995;10: 2938-2940.	Thyroid antibodies
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). European journal of obstetrics, gynecology, and reproductive biology 1997;74: 139-143.	Thyroid antibodies
Christiansen OB, Kolte AM, Dahl M, Larsen EC, Steffensen R, Nielsen HS, Hviid TV. Maternal homozygocity for a 14 base pair insertion in exon 8 of the HLA-G gene and carriage of HLA class II alleles restricting HY immunity predispose to unexplained secondary recurrent miscarriage and low birth weight in children born to these patients. Human immunology 2012;73: 699-705.	Overlap with other studies included
Christiansen OB, Mohapeloa HP, Steffensen R, Jersild C. HLA-C and -Bw typing of couples with unexplained recurrent miscarriages. Journal of reproductive immunology 1997;37: 63-77.	Small study
Christiansen OB, Riisom K, Lauritsen JG, Grunnet N. No increased histocompatibility antigen-sharing in couples with idiopathic habitual abortions. Human reproduction 1989;4: 160-162.	Small, older study
Christiansen OB, Ring M, Rosgaard A, Grunnet N, Gluud C. Association between HLA-DR1 and -DR3 antigens and unexplained repeated miscarriage. Human reproduction update 1999;5: 249-255.	More recent review available
Clark CA, Davidovits J, Spitzer KA, Laskin CA. The lupus anticoagulant: results from 2257 patients attending a high-risk pregnancy clinic. Blood 2013;122: 341-347; quiz 466.	Not relevant
Daher S, de Arruda Geraldes Denardi K, Blotta MH, Mamoni RL, Reck AP, Camano L, Mattar R. Cytokines in recurrent pregnancy loss. Journal of reproductive immunology 2004;62: 151-157.	Cytokine measured at unknown day of cycle

Dendrinos S, Papasteriades C, Tarassi K, Christodoulakos G, Prasinos G, Creatsas G. Thyroid autoimmunity in patients with recurrent spontaneous miscarriages. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2000;14: 270-274.	TPO ; thyroid function
Esplin MS, Branch DW, Silver R, Stagnaro-Green A. Thyroid autoantibodies are not associated with recurrent pregnancy loss. American journal of obstetrics and gynecology 1998;179: 1583-1586.	TPO
Garcia-De La Torre I, Hernandez-Vazquez L, Angulo-Vazquez J, Romero-Ornelas A. Prevalence of antinuclear antibodies in patients with habitual abortion and in normal and toxemic pregnancies. Rheumatology international 1984;4: 87-89.	Small study, non- consecutive pts
Gharesi-Fard B, Askarinejad-Behbahani R, Behdin S. The effect of HLA-DRB1 sharing between the couples with recurrent pregnancy loss on the pregnancy outcome after leukocyte therapy. Iranian journal of immunology : IJI 2014;11: 13-20.	Groups with miscarriage/birth retrospectively selected
Gharesi-Fard B, Jafarzadeh L, Zolghadri J, Haghbin H. Soluble CD30 in normal pregnancy, pre-eclampsia and recurrent pregnancy loss. Iranian journal of immunology : IJI 2012;9: 234-240.	Pilot study - Soluble CD30
Gloria-Bottini F, Nicotra M, Magrini A, Bottini E. Immunologic factors and reproductive success in women with primary repeated spontaneous abortion. Fertility and sterility 2010;93: 1014-1015.	SR on ANA available
Greaves M, Cohen H, MacHin SJ, Mackie I. Guidelines on the investigation and management of the antiphospholipid syndrome. British journal of haematology 2000;109: 704-715.	Guideline
Harger JH, Rabin BS, Marchese SG. The prognostic value of antinuclear antibodies in women with recurrent pregnancy losses: a prospective controlled study. Obstetrics and gynecology 1989;73: 419-424.	Non-pregn controls not comparable to patients
Hattori Y, Nakanishi T, Ozaki Y, Nozawa K, Sato T, Sugiura-Ogasawara M. Uterine cervical inflammatory cytokines, interleukin-6 and -8, as predictors of miscarriage in recurrent cases. American journal of reproductive immunology (New York, NY : 1989) 2007;58: 350-357.	Small number with misc. No karyotyping of misc. embryos
Houwert-de Jong MH, Termijtelen A, Eskes TK, Mantingh A, Bruinse HW. The natural course of habitual abortion. European journal of obstetrics, gynecology, and reproductive biology 1989;33: 221-228.	Few patients, serological typing, artificial control group
Hviid TV, Hylenius S, Hoegh AM, Kruse C, Christiansen OB. HLA-G polymorphisms in couples with recurrent spontaneous abortions. Tissue antigens 2002;60: 122-132.	Small study
Itsekson AM, Seidman DS, Zolti M, Lazarov A, Carp HJ. Recurrent pregnancy loss and inappropriate local immune response to sex hormones. American journal of reproductive immunology 2007;57: 160-165.	Subjective assessment of flare
Jaskowski TD, Wilson AR, Hill HR, Branch WD, Tebo AE. Autoantibodies against phosphatidylserine, prothrombin and phosphatidylserine-prothrombin complex: identical or distinct diagnostic tools for antiphospholipid syndrome? Clinica chimica acta; international journal of clinical chemistry 2009;410: 19-24.	Not relevant
Jasper MJ, Tremellen KP, Robertson SA. Reduced expression of IL-6 and IL-1alpha mRNAs in secretory phase endometrium of women with recurrent miscarriage. Journal of reproductive immunology 2007;73: 74-84.	Small study, measurements may be affected by previous birth in controls
Jin K, Ho HN, Speed TP, Gill TJ, 3rd. Reproductive failure and the major histocompatibility complex. American journal of human genetics 1995;56: 1456-1467.	Limited by use of serological methods
Kano T, Mori T, Furudono M, Ishikawa H, Watanabe H, Kikkawa E, Warita T, Onizuka M, Takahashi M, Maeda Y et al. Human leukocyte antigen may predict outcome of primary recurrent spontaneous abortion treated with paternal lymphocyte alloimmunization therapy. American journal of reproductive immunology 2007;58: 383-387.	Inconclusive, too small study for all these comparisons
Kishore R, Agarwal S, Halder A, Das V, Shukla BR, Agarwal SS. HLA sharing, anti-paternal cytotoxic antibodies and MLR blocking factors in	many RPL couples excluded

women with recurrent spontaneous abortion. The journal of obstetrics and gynaecology research 1996;22: 177-183.	
Kolho KL, Tiitinen A, Tulppala M, Unkila-Kallio L, Savilahti E. Screening for coeliac disease in women with a history of recurrent miscarriage or infertility. British journal of obstetrics and gynaecology 1999;106: 171-173.	Too small to provide useful information
Komlos L, Klein T, Korostishevsky M. HLA-A2 class I antigens in couples with recurrent spontaneous abortions. International journal of immunogenetics 2007;34: 241-246.	Small number, serological typing, multiple comparisons
Kovacs L, Szabo J, Molnar K, Kovacs A, Pokorny G. Antineutrophil cytoplasmic antibodies and other immunologic abnormalities in patients with habitual abortion. American journal of reproductive immunology 1999;41: 264-270.	Small number of controls
Krause M, Sonntag B, Klamroth R, Heinecke A, Scholz C, Langer C, Scharrer I, Greb RR, von Eckardstein A, Nowak-Gottl U. Lipoprotein (a) and other prothrombotic risk factors in Caucasian women with unexplained recurrent miscarriage. Results of a multicentre case-control study. Thrombosis and haemostasis 2005;93: 867-871.	Part of a extensive screening for thrombophilia factors
Kwak JY, Gilman-Sachs A, Beaman KD, Beer AE. Autoantibodies in women with primary recurrent spontaneous abortion of unknown etiology. Journal of reproductive immunology 1992;22: 15-31.	Extremely high APL ab levels Good age-stratification
Laitinen T, Lokki ML, Tulppala M, Ylikorkala O, Koskimies S. Increased frequency of complement C4 'null' alleles in recurrent spontaneous abortions. Human reproduction 1991;6: 1384-1387.	small study, controls not optimal
Laskin CA, Spitzer KA, Clark CA, Crowther MR, Ginsberg JS, Hawker GA, Kingdom JC, Barrett J, Gent M. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial Journal of rheumatology. 2009, pp. 279-287.	Irrelevant study: no information about importance of immune biomarkers
Lata K, Dutta P, Sridhar S, Rohilla M, Srinivasan A, Prashad GR, Shah VN, Bhansali A. Thyroid autoimmunity and obstetric outcomes in women with recurrent miscarriage: a case-control study. Endocrine connections 2013;2: 118-124.	TPO
Liu C, Wang XZ, Sun XB. Assessment of sperm antigen specific T regulatory cells in women with recurrent miscarriage. Early human development 2013;89: 95-100.	Unacceptable quality
Maier DB, Parke A. Subclinical autoimmunity in recurrent aborters. Fertility and sterility 1989;51: 280-285.	RPL as a marker for subclinical autoimmune disease.(small study)
Marai I, Carp H, Shai S, Shabo R, Fishman G, Shoenfeld Y. Autoantibody panel screening in recurrent miscarriages. American journal of reproductive immunology (New York, NY : 1989) 2004;51: 235-240.	TPO
McIntyre JA, Faulk WP, Nichols-Johnson VR, Taylor CG. Immunologic testing and immunotherapy in recurrent spontaneous abortion. Obstetrics and gynecology 1986;67: 169-175.	Flaws: use of serological testing and no clear definition of HLA sharing
Mecacci F, Parretti E, Cioni R, Lucchetti R, Magrini A, La Torre P, Mignosa M, Acanfora L, Mello G. 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. Journal of reproductive immunology 2000;46: 39-50.	TPO
Melk A, Mueller-Eckhardt G, Polten B, Lattermann A, Heine O, Hoffmann O. Diagnostic and prognostic significance of anticardiolipin antibodies in patients with recurrent spontaneous abortions. American journal of reproductive immunology 1995;33: 228-233.	anticardiolipin antibody
Muller AF, Verhoeff A, Mantel MJ, Berghout A. Thyroid autoimmunity and abortion: a prospective study in women undergoing in vitro fertilization. Fertility and sterility 1999;71: 30-34.	TPO and IVF
Nielsen HS, Christiansen OB. Prognostic impact of anticardiolipin antibodies in women with recurrent miscarriage negative for the lupus anticoagulant. Human reproduction 2005;20: 1720-1728.	anticardiolipin antibody
Obayashi S, Ozaki Y, Sugi T, Kitaori T, Katano K, Suzuki S, Sugiura-Ogasawara M. Antiphosphatidylethanolamine antibodies might not be an independent risk factor for further miscarriage in patients suffering	antiphosphatidylethanolamine antibodies

recurrent pregnancy loss. Journal of reproductive immunology 2010;85: 186-192.	
Ober C, Aldrich CL, Chervoneva I, Billstrand C, Rahimov F, Gray HL, Hyslop T. Variation in the HLA-G promoter region influences miscarriage rates. American journal of human genetics 2003;72: 1425-1435.	Not RPL
Ober C, Steck T, van der Ven K, Billstrand C, Messer L, Kwak J, Beaman K, Beer A. MHC class II compatibility in aborted fetuses and term infants of couples with recurrent spontaneous abortion. Journal of reproductive immunology 1993;25: 195-207.	Flaws: controls are previous RPL patients
Ogasawara M, Aoki K, Katano K, Aoyama T, Kajiura S, Suzumori K. Prevalence of autoantibodies in patients with recurrent miscarriages. American journal of reproductive immunology 1999;41: 86-90.	No comparison to controls
Oshiro BT, Silver RM, Scott JR, Yu H, Branch DW. Antiphospholipid antibodies and fetal death. Obstetrics and gynecology 1996;87: 489-493.	Not relevant
Out HJ, Bruinse HW, Christiaens GC, van Vliet M, Meilof JF, de Groot PG, Smeenk RJ, Derksen RH. Prevalence of antiphospholipid antibodies in patients with fetal loss. Annals of the rheumatic diseases 1991;50: 553-557.	Review on ANA available
Petri M, Golbus M, Anderson R, Whiting-O'Keefe Q, Corash L, Hellmann D. Antinuclear antibody, lupus anticoagulant, and anticardiolipin antibody in women with idiopathic habitual abortion. A controlled, prospective study of forty-four women. Arthritis Rheum 1987;30: 601-606.	Small number of controls
Pfeiffer KA, Fimmers R, Engels G, van der Ven H, van der Ven K. The HLA-G genotype is potentially associated with idiopathic recurrent spontaneous abortion. Molecular human reproduction 2001;7: 373-378.	Few patients in subgroups
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. Fertility and sterility 1993;60: 1001-1005.	TPO
Rai RS, Regan L, Clifford K, Pickering W, Dave M, Mackie I, McNally T, Cohen H. Antiphospholipid antibodies and beta 2-glycoprotein-I in 500 women with recurrent miscarriage: results of a comprehensive screening approach. Human reproduction 1995;10: 2001-2005.	Not relevant – no controls
Ramhorst RE, Garcia VE, Corigliano A, Etchepareborda JJ, Irigoyen M, Fainboim L. Expression of SLAM as a functional and phenotypic marker in women with recurrent miscarriage. Journal of reproductive immunology 2004;62: 139-149.	Small numbers Previous birth in controls can explain results
Regan L, Braude PR, Hill DP. A prospective study of the incidence, time of appearance and significance of anti-paternal lymphocytotoxic antibodies in human pregnancy. Human reproduction 1991;6: 294-298.	Not relevant
Rezaei A, Dabbagh A. T-helper (1) cytokines increase during early pregnancy in women with a history of recurrent spontaneous abortion. Medical science monitor : international medical journal of experimental and clinical research 2002;8: Cr607-610.	Some samples in RM women taken at time of miscarriage and may be caused by misc
Robert JM, Macara LM, Chalmers EA, Smith GC. Inter-assay variation in antiphospholipid antibody testing. BJOG : an international journal of obstetrics and gynaecology 2002;109: 348-349.	Not relevant
Roberts J, Jenkins C, Wilson R, Pearson C, Franklin IA, MacLean MA, McKillop JH, Walker JJ. Recurrent miscarriage is associated with increased numbers of CD5/20 positive lymphocytes and an increased incidence of thyroid antibodies. European journal of endocrinology 1996;134: 84-86.	Small study
Roussev RG, Kaider BD, Price DE, Coulam CB. Laboratory evaluation of women experiencing reproductive failure. American journal of reproductive immunology 1996;35: 415-420.	Unacceptable quality
Ruiz AM, Kwak JY, Kwak FM, Beer AE. Impact of age on reproductive outcome in women with recurrent spontaneous abortions and infertility of immune etiology. American journal of reproductive immunology 1996;35: 408-414.	Non-informative study
Ruiz JE, Cubillos J, Mendoza JC, Espinel FJ, Kwak JY, Beer AE. Autoantibodies to phospholipids and nuclear antigens in non-pregnant	Evidence on ANA from reviews available

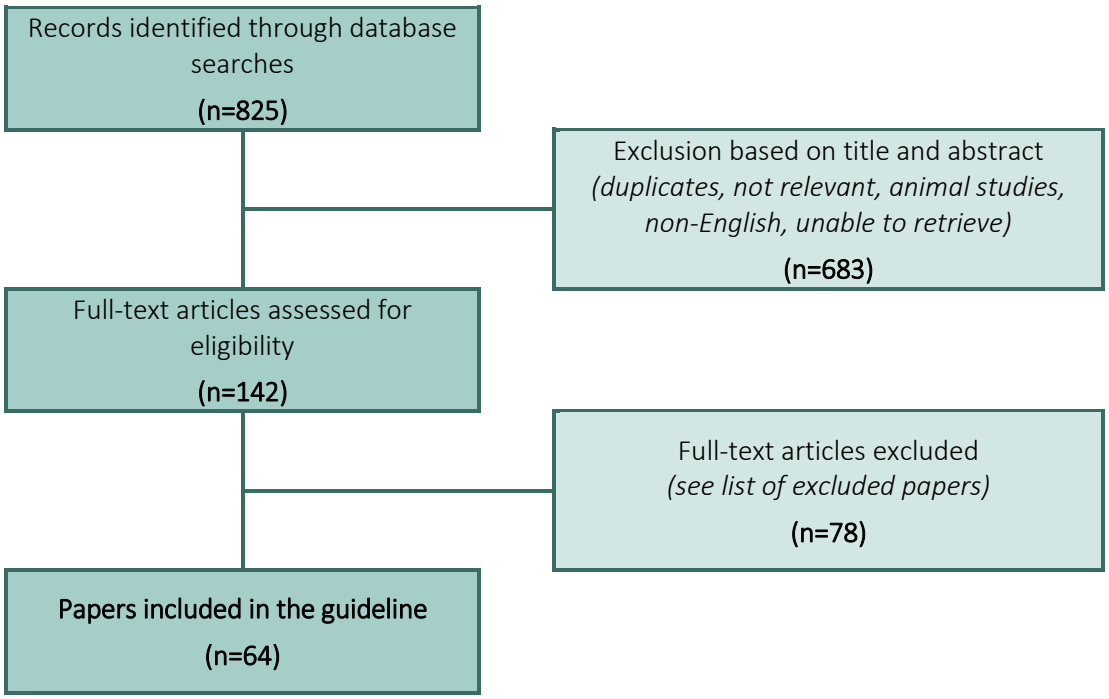
and pregnant Colombian women with recurrent spontaneous abortions. Journal of reproductive immunology 1995;28: 41-51.	
Rull K, Tomberg K, Koks S, Mannik J, Mols M, Sirotkina M, Varv S, Laan M. Increased placental expression and maternal serum levels of apoptosis-inducing TRAIL in recurrent miscarriage. Placenta 2013;34: 141-148.	A mixture of RM patients and patients with sporadic miscarriage
Rushworth FH, Backos M, Rai R, Chilcott IT, Baxter N, Regan L. Prospective pregnancy outcome in untreated recurrent miscarriers with thyroid autoantibodies. Human reproduction 2000;15: 1637-1639.	Not relevant for this question
Saeed Z, Haleh S, Afsaneh M, Soheila A, Amir Hassan Z, Farah I, Banafsheh T, Elham SS, Narges MB, Mahmood JT. Serum leptin levels in women with immunological recurrent abortion. Journal of reproduction & infertility 2010;11: 47-52.	Pos ANA part of the definition of immunological RPL
Sater MS, Finan RR, Mustafa FE, Al-Khateeb GM, Almawi WY. Anti-annexin V IgM and IgG autoantibodies and the risk of idiopathic recurrent spontaneous miscarriage. Journal of reproductive immunology 2011;89: 78-83.	RPL patients more obese than controls
Sbracia M, Mastrone M, Scarpellini F, Grasso JA. Influence of histocompatibility antigens in recurrent spontaneous abortion couples and on their reproductive performances. American journal of reproductive immunology 1996;35: 85-92.	Multiples comparisons in prevalence study.
Steffensen R, Christiansen OB, Bennett EP, Jersild C. HLA-E polymorphism in patients with recurrent spontaneous abortion. Tissue antigens 1998;52: 569-572.	HLA-E polymorphims unimportant in RM
Sugiura-Ogasawara M, Ozaki Y, Nakanishi T, Kumamoto Y, Suzumori K. Pregnancy outcome in recurrent aborters is not influenced by Chlamydia IgA and/or G. American journal of reproductive immunology 2005;53: 50-53.	antibodies against c. trachomatis,
Tebo AE, Jaskowski TD, Hill HR, Branch DW. Clinical relevance of multiple antibody specificity testing in anti-phospholipid syndrome and recurrent pregnancy loss. Clinical and experimental immunology 2008;154: 332-338.	Not relevant
Ticconi C, Giuliani E, Veglia M, Pietropolli A, Piccione E, Di Simone N. Thyroid autoimmunity and recurrent miscarriage. American journal of reproductive immunology 2011;66: 452-459.	TPO
Tripathi P, Abbas A, Naik S, Agrawal S. Role of 14-bp deletion in the HLA-G gene in the maintenance of pregnancy. Tissue antigens 2004;64: 706-710.	maintenance of pregnancy Huge exclusion of patients
Tulppala M, Palosuo T, Ramsay T, Miettinen A, Salonen R, Ylikorkala O. A prospective study of 63 couples with a history of recurrent spontaneous abortion: contributing factors and outcome of subsequent pregnancies. Human reproduction 1993;8: 764-770.	Not relevant for this question
Ulcova-Gallova Z, Krauz V, Novakova P, Milichovska L, Micanova Z, Bibkova K, Sucha R, Turek J, Balvin M, Rokyta Z. Anti-phospholipid antibodies against phosphatidylinositol, and phosphatidylserine are more significant in reproductive failure than antibodies against cardiolipin only. American journal of reproductive immunology (New York, NY : 1989) 2005;54: 112-117.	Control group poorly described
Unander AM, Norberg R, Arfors L, Enskog A, Haeger M, Lindholm A, Robbins D, Siosteen C, Soderstrom T, Stigendal L et al. Opinions on treatment of women with habitual abortion based on investigations for blocking antibody and autoantibodies. American journal of reproductive immunology 1991;26: 32-37.	Non-informative with regard to ANA
von Linsingen R, Bompeixe EP, Bicalho Mda G. A case-control study in IL6 and TGFB1 gene polymorphisms and recurrent spontaneous abortion in southern Brazilian patients. American journal of reproductive immunology (New York, NY : 1989) 2005;53: 94-99.	Mixed ethnicity (Brazil)
Vora S, Shetty S, Salvi V, Satoskar P, Ghosh K. Thrombophilia and unexplained pregnancy loss in Indian patients. The National medical journal of India 2008;21: 116-119.	Very low APS positivity in controls.

Wagenknecht DR, Green KM, McIntyre JA. Analyses of HLA-DQ alleles in recurrent spontaneous abortion (RSA) couples. American journal of reproductive immunology (New York, NY : 1989) 1997;37: 1-6.	Study flawed since patients were selected for being positive for HLA-A, -B and –DR sharing, which will affect the results
Xu B, Sun X, Li L, Wu L, Zhang A, Feng Y. Pinopodes, leukemia inhibitory factor, integrin-beta3, and mucin-1 expression in the peri-implantation endometrium of women with unexplained recurrent pregnancy loss. Fertility and sterility 2012;98: 389-395.	Differences may be caused by previous births in controls
Yan J, Sripada S, Saravelos SH, Chen ZJ, Egner W, Li TC. Thyroid peroxidase antibody in women with unexplained recurrent miscarriage: prevalence, prognostic value, and response to empirical thyroxine therapy. Fertility and sterility 2012;98: 378-382.	TPO
Yan WH, Fan LA, Yang JQ, Xu LD, Ge Y, Yao FJ. HLA-G polymorphism in a Chinese Han population with recurrent spontaneous abortion. International journal of immunogenetics 2006;33: 55-58.	Too small for conclusions
Yan WH, Lin A, Chen XJ, Dai MZ, Gan LH, Zhou MY, Zhu M, Shi WW, Liu JM. Association of the maternal 14-bp insertion polymorphism in the HLA-G gene in women with recurrent spontaneous abortions. Tissue antigens 2006;68: 521-523.	Some evidence that G14bp polymorphisms play a role in RM

Yellow marked paper not in ET as TPO was moved to other section

7. WHAT IS THE VALUE OF SCREENING FOR METABOLIC/ENDOCRINOLOGICAL ABNORMALITIES IN THE DIAGNOSIS OF RPL?

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Aubard Y, Darodes N, Cantaloube M. Hyperhomocysteinemia and pregnancy--review of our present understanding and therapeutic implications. European journal of obstetrics, gynecology, and reproductive biology 2000;93: 157-165.	Narrative review
Avivi I, Lanir N, Hoffman R, Brenner B. Hyperhomocysteinemia is common in patients with antiphospholipid syndrome and may contribute to expression of major thrombotic events. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis 2002;13: 169-172.	Hyperhomocysteinemia and APS
Baig S, Lim JY, Fernandis AZ, Wenk MR, Kale A, Su LL, Biswas A, Vasoo S, Shui G, Choolani M. Lipidomic analysis of human placental syncytiotrophoblast microvesicles in adverse pregnancy outcomes. Placenta 2013;34: 436-442.	Not relevant
Bellver J, Soares SR, Alvarez C, Munoz E, Ramirez A, Rubio C, Serra V, Remohi J, Pellicer A. The role of thrombophilia and thyroid autoimmunity in unexplained infertility, implantation failure and recurrent spontaneous abortion. Human reproduction 2008;23: 278-284.	included in review thangaratinam 2011 and review Van den Boogaard 2011
Boas WV, Goncalves RO, Costa OL, Goncalves MS. Metabolism and gene polymorphisms of the folate pathway in Brazilian women with history of recurrent abortion. Rev Bras Ginecol Obstet 2015;37: 71-76.	Hcy level according to genotype; Relevance unclear
Brenner B. Inherited thrombophilia and pregnancy loss. Best practice & research Clinical haematology 2003;16: 311-320.	Narrative review
Bulletti C, Flamigni C, Giacomucci E. Reproductive failure due to spontaneous abortion and recurrent miscarriage. Human reproduction update 1996;2: 118-136.	Selected THROMBOPHILIA
Bussen S, Steck T. Thyroid autoantibodies in euthyroid non-pregnant women with recurrent spontaneous abortions. Human reproduction 1995;10: 2938-2940.	included in review thangaratinam 2011
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). European journal of obstetrics, gynecology, and reproductive biology 1997;74: 139-143.	included in review thangaratinam 2011 and review Van den Boogaard 2011
Clifford K, Rai R, Watson H, Regan L. An informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases. Human reproduction 1994;9: 1328-1332.	no controls, no clear study population
Cocksedge KA, Li TC, Saravelos SH, Metwally M. A reappraisal of the role of polycystic ovary syndrome in recurrent miscarriage. Reproductive biomedicine online 2008;17: 151-160.	Non-systematic review
Coughlan C, Sinagra M, Ledger W, Li TC, Laird S. Endometrial integrin expression in women with recurrent implantation failure after in vitro fertilization and its relationship to pregnancy outcome. Fertility and sterility 2013;100: 825-830.	RIF not RPL
Coumans AB, Huijgens PC, Jakobs C, Schats R, de Vries JI, van Pampus MG, Dekker GA. Haemostatic and metabolic abnormalities in women with unexplained recurrent abortion. Human reproduction 1999;14: 211-214.	Included in meta-analysis Nelen 2000
Dal Lago A, Vaquero E, Pasqualetti P, Lazzarin N, De Carolis C, Perricone R, Moretti C. Prediction of early pregnancy maternal thyroid impairment in women affected with unexplained recurrent miscarriage. Human reproduction 2011;26: 1324-1330.	basic science study
De Vivo A, Mancuso A, Giacobbe A, Moleti M, Maggio Savasta L, De Dominici R, Priolo AM, Vermiglio F. Thyroid function in women found to have early pregnancy loss. Thyroid : official journal of the American Thyroid Association 2010;20: 633-637.	No controls
Dendrinos S, Papasteriades C, Tarassi K, Christodoulakos G, Prasinos G, Creatsas G. Thyroid autoimmunity in patients with recurrent spontaneous miscarriages. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2000;14: 270-274.	included in review thangaratinam 2011 and review Van den Boogaard 2011

Desjardins MK, Stephenson MD. "Information-rich" reproductive outcomes in carriers of a structural chromosome rearrangement ascertained on the basis of recurrent pregnancy loss. Fertility and sterility 2012;97: 894-903.	RPL with genetic background
Diejomaoh M, Jirous J, Al-Azemi M, Gupta M, Al-Jaber M, Farhat R, Mohd A. Insulin resistance in women with recurrent spontaneous miscarriage of unknown aetiology. Medical principles and practice 2007;16: 114-118.	Unacceptable quality
Dlugi AM. Hyperprolactinemic recurrent spontaneous pregnancy loss: a true clinical entity or a spurious finding? Fertility and sterility 1998;70: 253-255.	Editorial
Drakeley AJ, Quenby S, Farquharson RG. Mid-trimester loss--appraisal of a screening protocol. Human reproduction 1998;13: 1975-1980.	Unacceptable quality
Dukhovny S, Zutshi P, Abbott JF. Recurrent second trimester pregnancy loss: evaluation and management. Current opinion in endocrinology, diabetes, and obesity 2009;16: 451-458.	Non-systematic review
D'Uva M, Di Micco P, Strina I, Ranieri A, Alviggi C, Mollo A, Fabozzi F, Cacciapuoti L, di Frega MT, Iannuzzo M et al. Etiology of hypercoagulable state in women with recurrent fetal loss without other causes of miscarriage from Southern Italy: new clinical target for antithrombotic therapy. Biologics : targets & therapy 2008;2: 897-902.	No assessment of HHcy
D'Uva M, Micco PD, Strina I, Placido GD. Recurrent pregnancy loss and thrombophilia. Journal of clinical medicine research 2010;2: 18-22.	Narrative review
El-Far M, El-Sayed IH, El-Motwally AE, Hashem IA, Bakry N. Serum levels of TNF-alpha and antioxidant enzymes and placental TNF-alpha expression in unexplained recurrent spontaneous miscarriage. Journal of physiology and biochemistry 2009;65: 175-181.	Unacceptable quality
Erkenekli K, Sanhal CY, Yucel A, Bicer CK, Erel O, Uygur D. Thiol/disulfide homeostasis in patients with idiopathic recurrent pregnancy loss assessed by a novel assay: Report of a preliminary study. The journal of obstetrics and gynaecology research 2016;42: 136-141.	Preliminary study
Esplin MS, Branch DW, Silver R, Stagnaro-Green A. Thyroid autoantibodies are not associated with recurrent pregnancy loss. American journal of obstetrics and gynecology 1998;179: 1583-1586.	included in review thangaratinam 2011
Fedele L, Bianchi S. Habitual abortion: endocrinological aspects. Current opinion in obstetrics & gynecology 1995;7: 351-356.	Unacceptable quality
Garzia E, Borgato S, Cozzi V, Doi P, Bulfamante G, Persani L, Cetin I. Lack of expression of endometrial prolactin in early implantation failure: a pilot study. Human reproduction 2004;19: 1911-1916.	Pilot study
Germain AM, Romanik MC, Guerra I, Solari S, Reyes MS, Johnson RJ, Price K, Karumanchi SA, Valdes G. Endothelial dysfunction: a link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events? Hypertension 2007;49: 90-95.	Not relevant for question
Glinoer D. Thyroid immunity, thyroid dysfunction, and the risk of miscarriage: a propos article by Vaquero et al. Mild thyroid abnormalities and recurrent spontaneous abortion: diagnostic and therapeutical approach. American journal of reproductive immunology 2000;43: 202-203.	Non-systematic review
Gurbuz B, Yalti S, Ficicioglu C, Ozden S, Yildirim G, Sayar C. Basal hormone levels in women with recurrent pregnancy loss. Gynecological endocrinology 2003;17: 317-321.	Unacceptable quality – lack of controls
Hammond KR, Cataldo NA, Hubbard JA, Malizia BA, Steinkampf MP. Gestational hypothyroidism: development of mild hypothyroidism in early pregnancy in previously euthyroid women. Fertility and sterility 2015;103: 1532-1536.e1531.	Not on RPL
Harger JH, Archer DF, Marchese SG, Muracca-Clemens M, Garver KL. Etiology of recurrent pregnancy losses and outcome of subsequent pregnancies. Obstetrics and gynecology 1983;62: 574-581.	Unacceptable quality – lack of controls
Hensleigh PA, Fainstat T. Corpus luteum dysfunction: serum progesterone levels in diagnosis and assessment of therapy for recurrent and threatened abortion. Fertility and sterility 1979;32: 396-400.	Unacceptable quality
Hirahara F, Andoh N, Sawai K, Hirabuki T, Uemura T, Minaguchi H. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials. Fertility and sterility 1998;70: 246-252.	Unacceptable quality – lack of controls

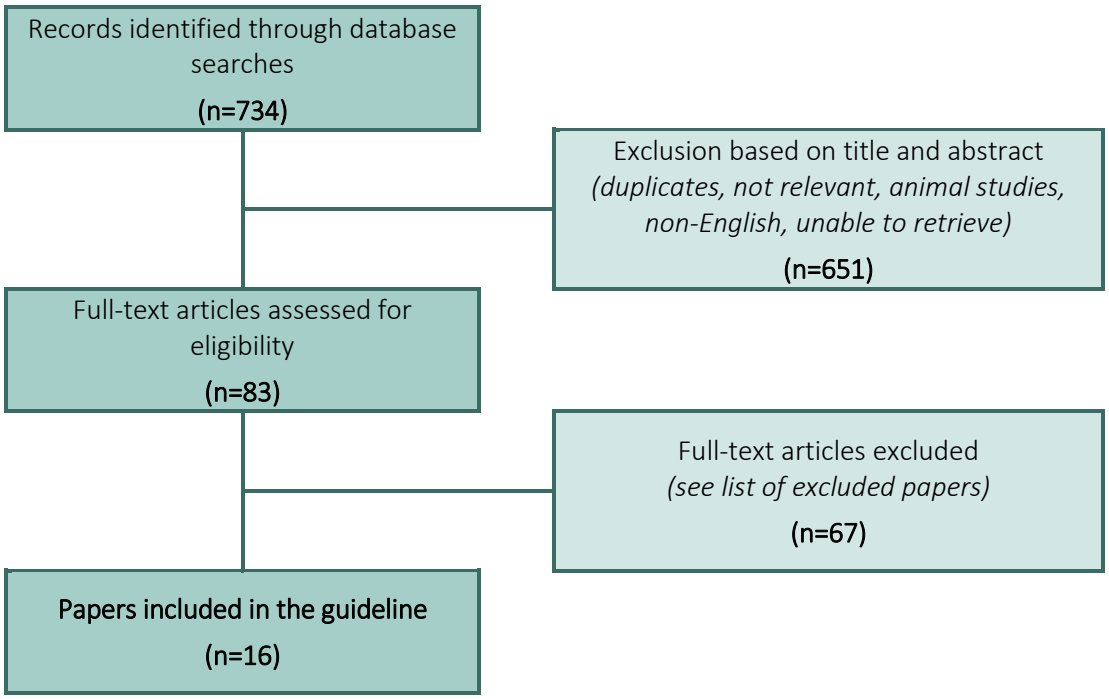
Holmes VA. Changes in haemostasis during normal pregnancy: does homocysteine play a role in maintaining homeostasis? The Proceedings of the Nutrition Society 2003;62: 479-493.	Narrative review of homocysteine in pregnancy
Igor S, Guilhem S, Isabelle RV. Stroke and recurrent pregnancy loss due to hyperhomocysteinaemia. European journal of neurology 2005;12: 235-236.	Case report
Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertility and sterility 2010;93: 1234-1243.	Unacceptable quality – lack of controls
Knabl J, Pestka A, Huttenbrenner R, Plosch T, Ensenauer R, Welbergen L, Hutter S, Gunthner-Biller M, Jeschke U. The liver x receptor in correlation with other nuclear receptors in spontaneous and recurrent abortions. PPAR research 2013;2013: 575604.	Unacceptable quality
Kuo PL, Guo HR. Mechanism of recurrent spontaneous abortions in women with mosaicism of X-chromosome aneuploidies. Fertility and sterility 2004;82: 1594-1601.	Primary question is not about ovarian reserve testing
Lee RM, Brown MA, Ward K, Nelson L, Branch DW, Silver RM. Homocysteine levels in women with antiphospholipid syndrome and normal fertile controls. Journal of reproductive immunology 2004;63: 23-30.	Homocysteine APS and normal fertile controls.- not RPL
Leigh AJ, Peattie AB. Polycystic ovaries and levels of gonadotrophins and androgens in recurrent miscarriage: prospective study in 50 women. British journal of obstetrics and gynaecology 1994;101: 275-276.	Not relevant for this question
McDonough PG. Repeated first-trimester pregnancy loss: evaluation and management. American journal of obstetrics and gynecology 1985;153: 1-6.	Unacceptable quality
Mecacci F, Parretti E, Cioni R, Lucchetti R, Magrini A, La Torre P, Mignosa M, Acanfora L, Mello G. 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. Journal of reproductive immunology 2000;46: 39-50.	included in review thangaratinam 2011 and review Van den Boogaard 2011
Motak-Pochrzest H, Malinowski A. The occurrence of immunological disturbances in patients with recurrent miscarriage (RM) of unknown etiology. Neuro endocrinology letters 2013;34: 701-707.	Not relevant for this question
Muller AF, Verhoeff A, Mantel MJ, Berghout A. Thyroid autoimmunity and abortion: a prospective study in women undergoing in vitro fertilization. Fertility and sterility 1999;71: 30-34.	Not relevant
Nadir Y, Hoffman R, Brenner B. Association of homocysteine, vitamin B12, folic acid, and MTHFR C677T in patients with a thrombotic event or recurrent fetal loss. Annals of hematology 2007;86: 35-40.	Mixed population, unclear relevance
Nelen WL, Blom HJ, Steegers EA, den Heijer M, Thomas CM, Eskes TK. Homocysteine and folate levels as risk factors for recurrent early pregnancy loss. Obstet Gynecol 2000;95: 519-524.	Included in meta-analysis Nelen 2000
Nelen WL, Bulten J, Steegers EA, Blom HJ, Hanselaar AG, Eskes TK. Maternal homocysteine and chorionic vascularization in recurrent early pregnancy loss. Hum Reprod 2000;15: 954-960.	basic science, not relevant for question
Nicotra M, Muttinelli C, Sbracia M, Rolfi G, Passi S. Blood levels of lipids, lipoperoxides, vitamin E and glutathione peroxidase in women with habitual abortion. Gynecologic and obstetric investigation 1994;38: 223-226.	Relevance for the question unclear
Peters AJ, Lloyd RP, Coulam CB. Prevalence of out-of-phase endometrial biopsy specimens. American journal of obstetrics and gynecology 1992;166: 1738-1745; discussion 1745-1736.	accuracy of histologic endometrial dating.
Plowden TC, Schisterman EF, Sjaarda LA, Zarek SM, Perkins NJ, Silver R, Galai N, DeCherney AH, Mumford SL. Subclinical hypothyroidism and thyroid autoimmunity are not associated with fecundity, pregnancy loss or live birth. The Journal of clinical endocrinology and metabolism 2016: jc20161049.	Not RPL women
Prakash A, Li TC, Tuckerman E, Laird S, Wells M, Ledger WL. A study of luteal phase expression of inhibin, activin, and follistatin subunits in the endometrium of women with recurrent miscarriage. Fertility and sterility 2006;86: 1723-1730.	Not relevant for this question
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. Fertility and sterility 1993;60: 1001-1005.	included in review thangaratinam 2011

Putowski L, Darmochwal-Kolarz D, Rolinski J, Oleszczuk J, Jakowicki J. The immunological profile of infertile women after repeated IVF failure (preliminary study). European journal of obstetrics, gynecology, and reproductive biology 2004;112: 192-196.	Not RPL women
Raziel A, Kornberg Y, Friedler S, Schachter M, Sela BA, Ron-El R. Hypercoagulable thrombophilic defects and hyperhomocysteinemia in patients with recurrent pregnancy loss. American journal of reproductive immunology 2001;45: 65-71.	Prevalence HHcy in controls not reported
Roberts J, Jenkins C, Wilson R, Pearson C, Franklin IA, MacLean MA, McKillop JH, Walker JJ. Recurrent miscarriage is associated with increased numbers of CD5/20 positive lymphocytes and an increased incidence of thyroid antibodies. European journal of endocrinology 1996;134: 84-86.	included in review Van den Boogaard 2011
Ronnenberg AG, Venners SA, Xu X, Chen C, Wang L, Guang W, Huang A, Wang X. Preconception B-vitamin and homocysteine status, conception, and early pregnancy loss. Am J Epidemiol 2007;166: 304-312.	Not RPL
Roque H, Paidas MJ, Funai EF, Kuczynski E, Lockwood CJ. Maternal thrombophilias are not associated with early pregnancy loss. Thrombosis and haemostasis 2004;91: 290-295.	HHcy is not discussed in the paper, except methodology
Rushworth FH, Backos M, Rai R, Chilcott IT, Baxter N, Regan L. Prospective pregnancy outcome in untreated recurrent miscarriers with thyroid autoantibodies. Human reproduction 2000;15: 1637-1639.	Not relevant for this question
Salker M, Teklenburg G, Molokhia M, Lavery S, Trew G, Aojanepong T, Mardon HJ, Lokugamage AU, Rai R, Landles C et al. Natural selection of human embryos: impaired decidualization of endometrium disables embryo-maternal interactions and causes recurrent pregnancy loss. PloS one 2010;5: e10287.	Endometrial prolactin – infertile couples as controls
Schachter M, Raziel A, Friedler S, Strassburger D, Bern O, Ron-El R. Insulin resistance in patients with polycystic ovary syndrome is associated with elevated plasma homocysteine. Hum Reprod 2003;18: 721-727.	Not RPL
Serle E, Aplin JD, Li TC, Warren MA, Graham RA, Seif MW, Cooke ID. Endometrial differentiation in the peri-implantation phase of women with recurrent miscarriage: a morphological and immunohistochemical study. Fertility and sterility 1994;62: 989-996.	Not relevant for this question
Shoham Z, Jacobs HS, Insler V. Luteinizing hormone: its role, mechanism of action, and detrimental effects when hypersecreted during the follicular phase. Fertility and sterility 1993;59: 1153-1161.	Non-systematic review
Skrzypczak J, Wirstlein P, Mikolajczyk M, Ludwikowski G, Zak T. TGF superfamily and MMP2, MMP9, TIMP1 genes expression in the endometrium of women with impaired reproduction. Folia histochemica et cytobiologica / Polish Academy of Sciences, Polish Histochemical and Cytochemical Society 2007;45 Suppl 1: S143-148.	Genetic study
Soules MR, McLachlan RI, Ek M, Dahl KD, Cohen NL, Bremner WJ. Luteal phase deficiency: characterization of reproductive hormones over the menstrual cycle. The Journal of clinical endocrinology and metabolism 1989;69: 804-812.	Not RPL
Stirrat GM. Recurrent miscarriage. II: Clinical associations, causes, and management. Lancet 1990;336: 728-733.	Non-systematic review
Sugiura-Ogasawara M, Ozaki Y, Nakanishi T, Kumamoto Y, Suzumori K. Pregnancy outcome in recurrent aborters is not influenced by Chlamydia IgA and/or G. American journal of reproductive immunology 2005;53: 50-53.	Not relevant for this question
Sugiura-Ogasawara M, Ozaki Y, Sonta S, Makino T, Suzumori K. Exposure to bisphenol A is associated with recurrent miscarriage. Human reproduction 2005;20: 2325-2329.	Not relevant for this question
Sugiura-Ogasawara M, Ozaki Y, Sonta S, Makino T, Suzumori K. PCBs, hexachlorobenzene and DDE are not associated with recurrent miscarriage. American journal of reproductive immunology 2003;50: 485-489.	Not relevant for this question
Tang AW, Alfirevic Z, Turner MA, Drury JA, Small R, Quenby S. A feasibility trial of screening women with idiopathic recurrent miscarriage for high uterine natural killer cell density and randomizing to prednisolone or placebo when pregnant Human reproduction . 2013, pp. 1743-1752.	Not relevant for this question
van Iddekinge B, Hofmeyr GJ. Recurrent spontaneous abortion--aetiological factors and subsequent reproductive performance in 76 couples. South	Unacceptable quality – lack of controls

African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 1991;80: 223-226.	
Vanrell JA, Balasch J. Luteal phase defects in repeated abortion. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 1986;24: 111-115.	Unacceptable quality
Vaquero E, Lazzarin N, De Carolis C, Valensise H, Moretti C, Ramanini C. Mild thyroid abnormalities and recurrent spontaneous abortion: diagnostic and therapeutical approach. American journal of reproductive immunology (New York, NY : 1989) 2000;43: 204-208.	Unacceptable quality – lack of controls
Wang Q, Luo L, Lei Q, Lin MM, Huang X, Chen MH, Zeng YH, Zhou CQ. Low aneuploidy rate in early pregnancy loss abortuses from patients with polycystic ovary syndrome. Reproductive biomedicine online 2016.	Not RPL
Yan J, Sripada S, Saravelos SH, Chen ZJ, Egner W, Li TC. Thyroid peroxidase antibody in women with unexplained recurrent miscarriage: prevalence, prognostic value, and response to empirical thyroxine therapy. Fertility and sterility 2012;98: 378-382.	Comparison of women with unexplained RPL versus those with known cause RPL
Yuen BH, Livingston JE, Poland BJ, Wittmann BK, Sy L, Cannon W. Human chorionic gonadotropin, estradiol, progesterone, prolactin, and B-scan ultrasound monitoring of complications in early pregnancy. Obstetrics and gynecology 1981;57: 207-214.	Unacceptable quality

8. WHAT IS THE VALUE OF ANATOMICAL INVESTIGATIONS IN THE DIAGNOSIS OF RPL?

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
AAGL practice report: practice guidelines for the diagnosis and management of submucous leiomyomas. J Minim Invasive Gynecol 2012;19: 152-171.	guideline
Abu-Musa A, Chahine R, Aridi O, Karam K. Successful pregnancy outcome following Tompkins metroplasty done early in pregnancy. Human reproduction 1998;13: 1387-1388.	Treatment – case report
ACOG Practice Bulletin No.142: Cerclage for the management of cervical insufficiency. Obstetrics and gynecology 2014;123: 372-379.	guideline
ACOG technology assessment no. 8: Sonohysterography. Obstetrics and gynecology 2012;119: 1325.	guideline
Alborzi S, Asadi N, Zolghadri J, Alborzi S, Alborzi M. Laparoscopic metroplasty in bicornuate and didelphic uteri. Fertility and sterility 2009;92: 352-355.	metroplasty – case report
Alessandrino F, Di Silverio E, Moramarco LP. Uterine arteriovenous malformation. Journal of ultrasound 2013;16: 41-44.	case report
Ayers JW, Peterson EP, Ansbacher R. Early therapy for the incompetent cervix in patients with habitual abortion. Fertility and sterility 1982;38: 177-181.	Medical intervention
Balasch J, Creus M, Vanrell JA. Lack of endometriosis in patients with repeated abortion. Human reproduction 1988;3: 263-264.	endometriosis
Ben-Nagi J, Miell J, Mavrelos D, Naftalin J, Lee C, Jurkovic D. Endometrial implantation factors in women with submucous uterine fibroids. Reproductive biomedicine online 2010;21: 610-615.	not RPL
Ben-Rafael Z, Seidman DS, Recabi K, Bider D, Mashiach S. Uterine anomalies. A retrospective, matched-control study. The Journal of reproductive medicine 1991;36: 723-727.	Not diagnostic
Bick RL, Madden J, Heller KB, Toofanian A. Recurrent miscarriage: causes, evaluation, and treatment. Medscape women's health 1998;3: 2.	narrative review

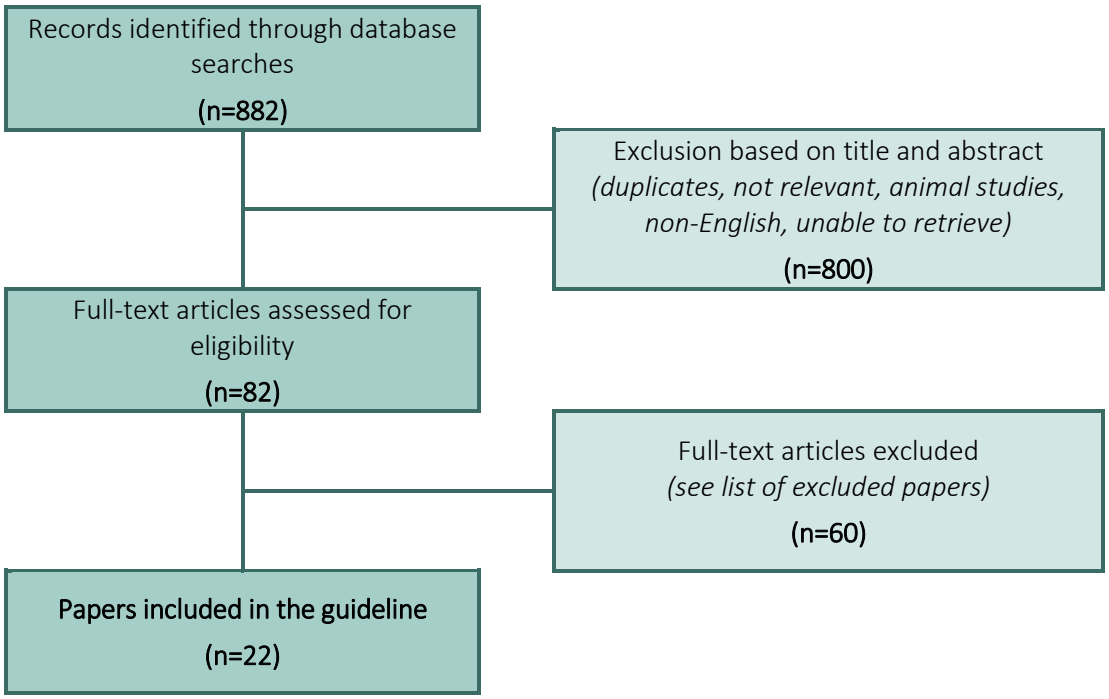
Bosteels J, Weyers S, Puttemans P, Panayotidis C, Van Herendael B, Gomel V, Mol BW, Mathieu C, D'Hooghe T. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review. Human reproduction update 2010;16: 1-11.	Treatment, in subfertile patients
Bottomley C, Van Belle V, Kirk E, Van Huffel S, Timmerman D, Bourne T. Accurate prediction of pregnancy viability by means of a simple scoring system. Human reproduction 2013;28: 68-76.	Not RPL
Branch DW, Gibson M, Silver RM. Clinical practice. Recurrent miscarriage. The New England journal of medicine 2010;363: 1740-1747.	treatment
Clifford K, Rai R, Watson H, Regan L. An informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases. Human reproduction 1994;9: 1328-1332.	not RPL
Cogendez E, Dolgun ZN, Sanverdi I, Turgut A, Eren S. Post-abortion hysteroscopy: a method for early diagnosis of congenital and acquired intrauterine causes of abortions. European journal of obstetrics, gynecology, and reproductive biology 2011;156: 101-104.	Incidence of Uterine abnormalities with HSC
Colacurci N, De Placido G, Mollo A, Carravetta C, De Franciscis P. Reproductive outcome after hysteroscopic metroplasty. European journal of obstetrics, gynecology, and reproductive biology 1996;66: 147-150.	HSC metroplasty (resectoscope)
El-Sherbiny W, El-Mazny A, Abou-Salem N, Mostafa WS. The diagnostic accuracy of two- versus three-dimensional sonohysterography for evaluation of the uterine cavity in the reproductive age. J Minim Invasive Gynecol 2014.	some of the patients had RM
Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertility and sterility 2012;98: 1103-1111.	committee opinion
Fernandez H, Garbin O, Castaigne V, Gervaise A, Levaillant JM. Surgical approach to and reproductive outcome after surgical correction of a T-shaped uterus. Human reproduction 2011;26: 1730-1734.	Not relevant for this question
France JT, Keelan J, Song L, Liddell H, Zanderigo A, Knox B. Serum concentrations of human chorionic gonadotrophin and immunoreactive inhibin in early pregnancy and recurrent miscarriage: a longitudinal study. The Australian & New Zealand journal of obstetrics & gynaecology 1996;36: 325-330.	Not relevant for this question
Ghahiry AA, Refaei Aliabadi E, Taherian AA, Najafian A, Ghasemi M. Effectiveness of hysteroscopic repair of uterine lesions in reproductive outcome. International journal of fertility & sterility 2014;8: 129-134.	Not relevant for this question
Goldberg JM, Falcone T, Attaran M. Sonohysterographic evaluation of uterine abnormalities noted on hysterosalpingography. Human reproduction 1997;12: 2151-2153.	Low number of patients, one single group with infertility and RPL
Gopal M, Goldberg J, Klein TA, Fossum GT. Embolization of a uterine arteriovenous malformation followed by a twin pregnancy. Obstetrics and gynecology 2003;102: 696-698.	Case report
Guimaraes Filho HA, Mattar R, Pires CR, Araujo Junior E, Moron AF, Nardozza LM. Comparison of hysterosalpingography, hysterosonography and hysteroscopy in evaluation of the uterine cavity in patients with recurrent pregnancy losses. Archives of gynecology and obstetrics 2006;274: 284-288.	Included in review Saravelos 2008
Homer HA, Li TC, Cooke ID. The septate uterus: a review of management and reproductive outcome. Fertility and sterility 2000;73: 1-14.	Non-systematic review
Ignatov A, Costa SD, Kleinstein J. Reproductive outcome of women with rare Mullerian anomaly: report of 2 cases. J Minim Invasive Gynecol 2008;15: 502-504.	case report – not RPL
Itzkowic DJ, Bennett MJ. Hysteroscopic metroplasty. The Australian & New Zealand journal of obstetrics & gynaecology 1988;28: 305-306.	Not relevant for this question
Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertility and sterility 2010;93: 1234-1243.	Prevalence uterine malformations in RM – more recent review Jaslow 2013 available
Jauniaux E, Farquharson RG, Christiansen OB, Exalto N. Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. Human reproduction 2006;21: 2216-2222.	Previous RPL Guideline
Jurkovic D, Geipel A, Gruboeck K, Jauniaux E, Natucci M, Campbell S. Three-dimensional ultrasound for the assessment of uterine anatomy and detection of congenital anomalies: a comparison with	Low number of patients. Old paper, Ultrasound machines are even more precise now

hysterosalpingography and two-dimensional sonography. Ultrasound in obstetrics & gynecology 1995;5: 233-237.	
Keltz MD, Olive DL, Kim AH, Arici A. Sonohysterography for screening in recurrent pregnancy loss. Fertility and sterility 1997;67: 670-674.	Included in review Saravelos 2008
Kowalik CR, Goddijn M, Emanuel MH, Bongers MY, Spinder T, de Kruif JH, Mol Ben Willem J, Heineman Maas J. Metroplasty versus expectant management for women with recurrent miscarriage and a septate uterus Cochrane Database of Systematic Reviews. 2011. John Wiley & Sons, Ltd.	Meta-analysis metroplasty
Kucuk T, Deveci S. "Chromohysteroscopy" for evaluation of endometrium in recurrent miscarriage. Clinical and experimental obstetrics & gynecology 2008;35: 133-136.	chromoHSC is not a standard technique
Lazzarin N, Exacoustos C, Vaquero E, De Felice G, Manfellotto D, Zupi E. Uterine junctional zone at three-dimensional transvaginal ultrasonography in patients with recurrent miscarriage: a new diagnostic tool? European journal of obstetrics, gynecology, and reproductive biology 2014;174: 128-132.	Subendometrial thickness is not standarized
Leible S, Cumsille F, Walton R, Munoz H, Jankelevich J, Sepulveda W. Discordant uterine artery velocity waveforms as a predictor of subsequent miscarriage in early viable pregnancies. American journal of obstetrics and gynecology 1998;179: 1587-1593.	Old paper
March CM, Israel R. Hysteroscopic management of recurrent abortion caused by septate uterus. American journal of obstetrics and gynecology 1987;156: 834-842.	non homogeneous group, without outcome analysis in RM patients
Nakatsuka M, Habara T, Noguchi S, Konishi H, Kudo T. Impaired uterine arterial blood flow in pregnant women with recurrent pregnancy loss. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 2003;22: 27-31.	Patients with RM in this paper were receiving treatment with LMWH and aspirin
Nawroth F, Foth D. One-stop recurrent miscarriage clinic and hysteroscopy--an urgent combination? Human reproduction 2005;20: 2976-2979.	Not relevant for this question
Olpin JD, Heilbrun M. Imaging of Mullerian duct anomalies. Clinical obstetrics and gynecology 2009;52: 40-56.	Non-systematic review
Olpin JD, Heilbrun M. Imaging of Mullerian duct anomalies. Topics in magnetic resonance imaging : TMRI 2010;21: 225-235.	not RPL population
Paradisi R, Barzanti R, Natali F, Battaglia C, Venturoli S. Metroplasty in a large population of women with septate uterus. J Minim Invasive Gynecol 2011;18: 449-454.	treatment
Pelosi MA. Laparoscopic Assisted Vaginal Metroplasty. The Journal of the American Association of Gynecologic Laparoscopists 1994;1: S28.	Case report
Portuondo JA, Camara MM, Echanojauregui AD, Calonge J. Mullerian abnormalities in fertile women and recurrent aborters. The Journal of reproductive medicine 1986;31: 616-619.	Old paper
Proctor JA, Haney AF. Recurrent first trimester pregnancy loss is associated with uterine septum but not with bicornuate uterus. Fertility and sterility 2003;80: 1212-1215.	Similar data available in systematic review
Rackow BW, Arici A. Reproductive performance of women with mullerian anomalies. Current opinion in obstetrics & gynecology 2007;19: 229-237.	Non-systematic review
Raziel A, Arieli S, Bukovsky I, Caspi E, Golan A. Investigation of the uterine cavity in recurrent aborters. Fertility and sterility 1994;62: 1080-1082.	HSG vs hysteroscopy
Romer T. Post-abortion-hysteroscopy--a method for early diagnosis of congenital and acquired intrauterine causes of abortions. European journal of obstetrics, gynecology, and reproductive biology 1994;57: 171-173.	Not relevant for question
Roy KK, Singla S, Baruah J, Sharma JB, Kumar S, Singh N. Reproductive outcome following hysteroscopic myomectomy in patients with infertility and recurrent abortions. Archives of gynecology and obstetrics 2010;282: 553-560.	myomectomy
Salim R, Jurkovic D. Assessing congenital uterine anomalies: the role of three-dimensional ultrasonography. Best practice & research Clinical obstetrics & gynaecology 2004;18: 29-36.	Non-systematic review
Saravelos SH, Cocksedge KA, Li TC. The pattern of pregnancy loss in women with congenital uterine anomalies and recurrent miscarriage. Reproductive biomedicine online 2010;20: 416-422.	Relevance unclear

Seckin B, Sarikaya E, Oruc AS, Celen S, Cicek N. Office hysteroscopic findings in patients with two, three, and four or more, consecutive miscarriages. The European journal of contraception & reproductive health care 2012;17: 393-398.	Similar data available in systematic review
Shawki HE. Reproductive outcomes after Versapoint hysteroscopic metroplasty Middle East Fertility Society Journal. 2010, pp. 259-264.	Small study
Sugiura-Ogasawara M, Ozaki Y, Suzumori N. Mullerian anomalies and recurrent miscarriage. Current opinion in obstetrics & gynecology 2013;25: 293-298.	Non-systematic review
Troiano RN, McCarthy SM. Mullerian duct anomalies: imaging and clinical issues. Radiology 2004;233: 19-34.	Non-systematic review
Tulppala M, Palosuo T, Ramsay T, Miettinen A, Salonen R, Ylikorkala O. A prospective study of 63 couples with a history of recurrent spontaneous abortion: contributing factors and outcome of subsequent pregnancies. Human reproduction 1993;8: 764-770.	Older paper
Valenzano MM, Mistrangelo E, Lijoi D, Fortunato T, Lantieri PB, Risso D, Costantini S, Ragni N. Transvaginal sonohysterographic evaluation of uterine malformations. European journal of obstetrics, gynecology, and reproductive biology 2006;124: 246-249.	Included in review Saravelos
Valle RF, Sciarra JJ. Hysteroscopic treatment of the septate uterus. Obstetrics and gynecology 1986;67: 253-257.	low number of cases
Valli E, Vaquero E, Lazzarin N, Caserta D, Marconi D, Zupi E. Hysteroscopic metroplasty improves gestational outcome in women with recurrent spontaneous abortion. The Journal of the American Association of Gynecologic Laparoscopists 2004;11: 240-244.	metroplasty
Valli E, Zupi E, Marconi D, Vaquero E, Giovannini P, Lazzarin N, Romanini C. Hysteroscopic findings in 344 women with recurrent spontaneous abortion. The Journal of the American Association of Gynecologic Laparoscopists 2001;8: 398-401.	Similar data available in systematic review
Ventolini G, Zhang M, Gruber J. Hysteroscopy in the evaluation of patients with recurrent pregnancy loss: a cohort study in a primary care population. Surgical endoscopy 2004;18: 1782-1784.	Similar data available in systematic review
Vercammen EE, D'Hooghe TM. Endometriosis and recurrent pregnancy loss. Seminars in reproductive medicine 2000;18: 363-368.	Non-systematic review
Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. Human reproduction 2014;29: 964-977.	IVF, not RPL
Vercellini P, Ragni G, Trespidi L, Oldani S, Panazza S, Crosignani PG. A modified technique for correction of the complete septate uterus. Acta obstetricia et gynecologica Scandinavica 1994;73: 425-428.	treatment
Zafarani F, Ahmadi F. Evaluation of intrauterine structural pathology by three-dimensional sonohysterography using an extended imaging method. International journal of fertility & sterility 2013;7: 1-6.	Descriptive paper
Zolghadri J, Momtahan M, Alborzi S, Mohammadinejad A, Khosravi D. Pregnancy outcome in patients with early recurrent abortion following laparoscopic tubal corneal interruption of a fallopian tube with hydrosalpinx. Fertility and sterility 2006;86: 149-151.	treatment
Zolghadri J, Momtahan M, Aminian K, Ghaffarpasand F, Tavana Z. The value of hysteroscopy in diagnosis of chronic endometritis in patients with unexplained recurrent spontaneous abortion. European journal of obstetrics, gynecology, and reproductive biology 2011;155: 217-220.	endometritis

9. WHAT IS THE VALUE OF MALE SCREENING IN THE DIAGNOSIS OF RPL?

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Absalan F, Ghannadi A, Kazerooni M, Parifar R, Jamalzadeh F, Amiri S. Value of sperm chromatin dispersion test in couples with unexplained recurrent abortion. Journal of assisted reproduction and genetics 2012;29: 11-14.	Not relevant
Al-Hassan S, Hellani A, Al-Shahrani A, Al-Deery M, Jaroudi K, Coskun S. Sperm chromosomal abnormalities in patients with unexplained recurrent abortions. Archives of andrology 2005;51: 69-76.	Small study
Ankolkar M, Patil A, Warke H, Salvi V, Kedia Mokashi N, Pathak S, Balasinor NH. Methylation analysis of idiopathic recurrent spontaneous miscarriage cases reveals aberrant imprinting at H19 ICR in normozoospermic individuals. Fertility and sterility 2012;98: 1186-1192.	Not relevant
Ankolkar M, Salvi V, Warke H, Vundinti BR, Balasinor NH. Methylation status of imprinted genes DLK1-GTL2, MEST (PEG1), ZAC (PLAGL1), and LINE-1 elements in spermatozoa of normozoospermic men, unlike H19 imprinting control regions, is not associated with idiopathic recurrent spontaneous miscarriages. Fertility and sterility 2013;99: 1668-1673.	Not relevant
Asadpor U, Totonchi M, Sabbaghian M, Hoseinifar H, Akhound MR, Zari Moradi S, Haratian K, Sadighi Gilani MA, Gourabi H, Mohseni Meybodi A. Ubiquitin-specific protease (USP26) gene alterations associated with male infertility and recurrent pregnancy loss (RPL) in Iranian infertile patients. Journal of assisted reproduction and genetics 2013;30: 923-931.	Not relevant
Bahceci M, Ulug U. Does underlying infertility aetiology impact on first trimester miscarriage rate following ICSI? A preliminary report from 1244 singleton gestations. Human reproduction 2005;20: 717-721.	Not RPL
Bellver J, Meseguer M, Muriel L, Garcia-Herrero S, Barreto MA, Garda AL, Remohi J, Pellicer A, Garrido N. Y chromosome microdeletions, sperm DNA fragmentation and sperm oxidative stress as causes of recurrent	Included in review Robinson 2012

spontaneous abortion of unknown etiology. Human reproduction 2010;25: 1713-1721.	
Bhattacharya SM. Hypo-osmotic swelling test and unexplained repeat early pregnancy loss. The journal of obstetrics and gynaecology research 2010;36: 119-122.	Not relevant
Borini A, Tarozzi N, Bizzaro D, Bonu MA, Fava L, Flamigni C, Coticchio G. Sperm DNA fragmentation: paternal effect on early post-implantation embryo development in ART. Human reproduction 2006;21: 2876-2881.	Included in review Robinson 2012 and Zhao 2014
Buckett WM, Luckas MJ, Aird IA, Farquharson RG, Kingsland CR, Lewis-Jones DI. The hypo-osmotic swelling test in recurrent miscarriage. Fertility and sterility 1997;68: 506-509.	Small study
Caramins MC, Saville T, Shakeshaft R, Mullan GL, Miller B, Yip MY, Buckley MF. A comparison of molecular and cytogenetic techniques for the diagnosis of pregnancy loss. Genetics in medicine : official journal of the American College of Medical Genetics 2011;13: 46-51.	Study on genetics
Carrell DT, Liu L, Peterson CM, Jones KP, Hatasaka HH, Erickson L, Campbell B. Sperm DNA fragmentation is increased in couples with unexplained recurrent pregnancy loss. Archives of andrology 2003;49: 49-55.	Small study
Carrell DT, Wilcox AL, Lowy L, Peterson CM, Jones KP, Erickson L, Campbell B, Branch DW, Hatasaka HH. Elevated sperm chromosome aneuploidy and apoptosis in patients with unexplained recurrent pregnancy loss. Obstetrics and gynecology 2003;101: 1229-1235.	Small study
Collodel G, Giannerini V, Antonio Pascarelli N, Federico MG, Comodo F, Moretti E. TEM and FISH studies in sperm from men of couples with recurrent pregnancy loss. Andrologia 2009;41: 352-360.	Not relevant for question
Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T, Cutting R, Ong K, Sallam H, Li TC. Recurrent implantation failure: definition and management. Reproductive biomedicine online 2014;28: 14-38.	Not RPL
Dul EC, van Echten-Arends J, Groen H, Dijkhuizen T, Land JA, van Ravenswaaij-Arts CM. Chromosomal abnormalities in azoospermic and non-azoospermic infertile men: numbers needed to be screened to prevent adverse pregnancy outcomes. Human reproduction 2012;27: 2850-2856.	Not RPL
Egozcue S, Blanco J, Vendrell JM, Garcia F, Veiga A, Aran B, Barri PN, Vidal F, Egozcue J. Human male infertility: chromosome anomalies, meiotic disorders, abnormal spermatozoa and recurrent abortion. Human reproduction update 2000;6: 93-105.	Inadequate data
Enciso M, Alfarawati S, Wells D. Increased numbers of DNA-damaged spermatozoa in samples presenting an elevated rate of numerical chromosome abnormalities. Human reproduction 2013;28: 1707-1715.	Not RPL
Gil-Villa AM, Cardona-Maya W, Agarwal A, Sharma R, Cadavid A. Assessment of sperm factors possibly involved in early recurrent pregnancy loss. Fertility and sterility 2010;94: 1465-1472.	Small study
Giorlandino C, Calugi G, Iaconianni L, Santoro ML, Lippa A. Spermatozoa with chromosomal abnormalities may result in a higher rate of recurrent abortion. Fertility and sterility 1998;70: 576-577.	Case report
Gopalkrishnan K, Hurkadli K, Padwal V, Balaiah D. Use of acridine orange to evaluate chromatin integrity of human spermatozoa in different groups of infertile men. Andrologia 1999;31: 277-282.	Not relevant
Hill JA, Abbott AF, Politch JA. Sperm morphology and recurrent abortion. Fertility and sterility 1994;61: 776-778.	Not relevant
Hill JA, Anderson DJ, Polgar K, Abbott AF, Politch JA. Seminal white blood cells and recurrent abortion. Human reproduction 1994;9: 1180-1183.	Not relevant
Honda H, Miharu N, Ohashi Y, Honda N, Hara T, Ohama K. Analysis of segregation and aneuploidy in two reciprocal translocation carriers, t(3;9)(q26.2;q32) and t(3;9)(p25;q32), by triple-color fluorescence in situ hybridization. Human genetics 1999;105: 428-436.	Case report
Kazerooni T, Asadi N, Jadid L, Kazerooni M, Ghanadi A, Ghaffarpasand F, Kazerooni Y, Zolghadr J. Evaluation of sperm's chromatin quality with acridine orange test, chromomycin A3 and aniline blue staining in couples with unexplained recurrent abortion. Journal of assisted reproduction and genetics 2009;26: 591-596.	Not relevant

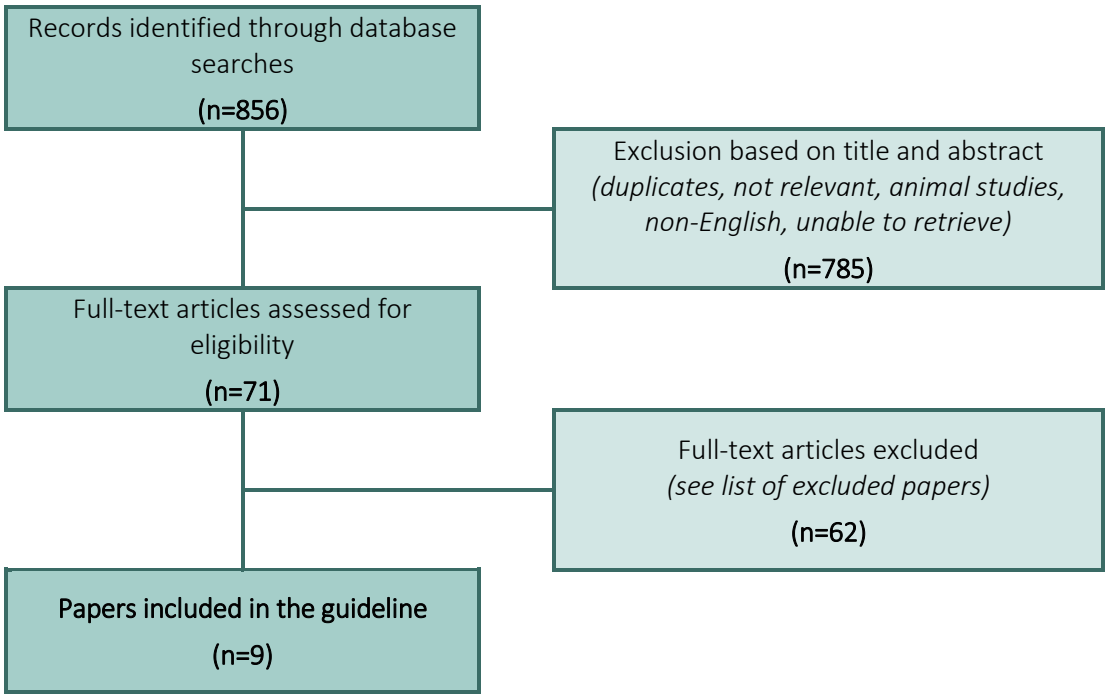
Kumar K, Deka D, Singh A, Chattopadhyay P, Dada R. Expression pattern of PRM2, HSP90 and WNT5A in male partners of couples experiencing idiopathic recurrent miscarriages. Journal of genetics 2012;91: 363-366.	Not relevant
Kumar K, Deka D, Singh A, Mitra DK, Vanitha BR, Dada R. Predictive value of DNA integrity analysis in idiopathic recurrent pregnancy loss following spontaneous conception. Journal of assisted reproduction and genetics 2012;29: 861-867.	Not relevant
Kumar K, Thilagavathi J, Deka D, Dada R. Unexplained early pregnancy loss: role of paternal DNA. The Indian journal of medical research 2012;136: 296-298.	letter
Kushnir VA, Frattarelli JL. Aneuploidy in abortuses following IVF and ICSI. Journal of assisted reproduction and genetics 2009;26: 93-97.	Not relevant
Larsen EC, Christiansen OB, Kolte AM, Macklon N. New insights into mechanisms behind miscarriage. BMC medicine 2013;11: 154.	Not an original study
Mansour Ghanaie M, Asgari SA, Dadrass N, Allahkhah A, Iran-Pour E, Safarinejad MR. Effects of varicocele repair on spontaneous first trimester miscarriage: a randomized clinical trial. Urology journal 2012;9: 505-513.	Treatment study
Mathur S, Baker ER, Williamson HO, Derrick FC, Teague KJ, Fudenberg HH. Clinical significance of sperm antibodies in infertility. Fertility and sterility 1981;36: 486-495.	Inadequate data
Molinari E, Mirabelli M, Raimondo S, Brussino A, Gennarelli G, Bongioanni F, Revelli A. Sperm macrocephaly syndrome in a patient without AURKC mutations and with a history of recurrent miscarriage. Reproductive biomedicine online 2013;26: 148-156.	Case report
Nabi A, Khalili MA, Halvaei I, Ghasemzadeh J, Zare E. Seminal bacterial contaminations: Probable factor in unexplained recurrent pregnancy loss. Iranian journal of reproductive medicine 2013;11: 925-932.	Seminal bacterial contaminations not discussed in the guideline (1 small study)
Pons I, Cercas R, Villas C, Brana C, Fernandez-Shaw S. One abstinence day decreases sperm DNA fragmentation in 90 % of selected patients. Journal of assisted reproduction and genetics 2013;30: 1211-1218.	No data on pregnancy loss
Rao L, Murthy K, Babu A, Venkata P, Deenadayal M, Singh L. Chromosome inversions and a novel chromosome insertion associated with recurrent miscarriages in South India. Archives of gynecology and obstetrics 2005;272: 273-277.	Not relevant
Ribas-Maynou J, Garcia-Peiro A, Fernandez-Encinas A, Amengual MJ, Prada E, Cortes P, Navarro J, Benet J. Double stranded sperm DNA breaks, measured by Comet assay, are associated with unexplained recurrent miscarriage in couples without a female factor. PloS one 2012;7: e44679.	Small study
Robinson WP, McFadden DE, Stephenson MD. The origin of abnormalities in recurrent aneuploidy/polyploidy. American journal of human genetics 2001;69: 1245-1254.	Not relevant
Rotondo JC, Bosi S, Bazzan E, Di Domenico M, De Mattei M, Selvatici R, Patella A, Marci R, Tognon M, Martini F. Methylenetetrahydrofolate reductase gene promoter hypermethylation in semen samples of infertile couples correlates with recurrent spontaneous abortion. Human reproduction 2012;27: 3632-3638.	Relevance of hypermethylation of MTHFR for RPL is unclear
Rubio C, Gil-Salom M, Simon C, Vidal F, Rodrigo L, Minguez Y, Remohi J, Pellicer A. Incidence of sperm chromosomal abnormalities in a risk population: relationship with sperm quality and ICSI outcome. Human reproduction 2001;16: 2084-2092.	Not RPL
Rubio C, Simon C, Blanco J, Vidal F, Minguez Y, Egozcue J, Crespo J, Remohi J, Pellicer A. Implications of sperm chromosome abnormalities in recurrent miscarriage. Journal of assisted reproduction and genetics 1999;16: 253-258.	Small studies, 12 sperm samples
Sachs ES, Jahoda MG, Van Hemel JO, Hoogeboom AJ, Sandkuyl LA. Chromosome studies of 500 couples with two or more abortions. Obstetrics and gynecology 1985;65: 375-378.	Old study
Saxena P, Misro MM, Chaki SP, Chopra K, Roy S, Nandan D. Is abnormal sperm function an indicator among couples with recurrent pregnancy loss? Fertility and sterility 2008;90: 1854-1858.	Comparison of RPL with normal and abnormal sperm

Saxena P, Misro MM, Roy S, Chopra K, Sinha D, Nandan D, Trivedi SS. Possible role of male factors in recurrent pregnancy loss. Indian journal of physiology and pharmacology 2008;52: 274-282.	Similar to Saxena F&S 2008
Schwartz D, Mayaux MJ, Guihard-Moscato ML, Czyglik F, David G. Abortion rate in A.I.D. and semen characteristics: a study of 1345 pregnancies. Andrologia 1986;18: 292-298.	Inadequate data
Shamsi MB, Venkatesh S, Pathak D, Deka D, Dada R. Sperm DNA damage & oxidative stress in recurrent spontaneous abortion (RSA). The Indian journal of medical research 2011;133: 550-551.	Small study
Sider D, Wilson WG, Sudduth K, Atkin JF, Kelly TE. Cytogenetic studies in couples with recurrent pregnancy loss. Southern medical journal 1988;81: 1521-1524.	Old study
Somprasit C, Aguinaga M, Cisneros PL, Torsky S, Carson SA, Buster JE, Amato P, McAdoo SL, Simpson JL, Bischoff FZ. Paternal gonadal mosaicism detected in a couple with recurrent abortions undergoing PGD: FISH analysis of sperm nuclei proves valuable. Reproductive biomedicine online 2004;9: 225-230.	Case report
Stouffs K, Vandermaelen D, Tournaye H, Liebaers I, Lissens W. Mutation analysis of three genes in patients with maturation arrest of spermatogenesis and couples with recurrent miscarriages. Reproductive biomedicine online 2011;22: 65-71.	Not relevant
Tatarinov YS, Posiseeva LV, Belyankin EV. Human protein factor of fertility and spontaneous abortion. Gynecologic and obstetric investigation 1993;35: 140-142.	Inadequate data and quality
Thilagavathi J, Mishra SS, Kumar M, Vemprala K, Deka D, Dhadwal V, Dada R. Analysis of telomere length in couples experiencing idiopathic recurrent pregnancy loss. Journal of assisted reproduction and genetics 2013;30: 793-798.	Not relevant
Trappe R, Bohm D, Kohlhase J, Weise A, Liehr T, Essers G, Meins M, Zoll B, Bartels I, Burfeind P. A novel family-specific translocation t(2;20)(p24.1;q13.1) associated with recurrent abortions: molecular characterization and segregation analysis in male meiosis. Cytogenetic and genome research 2002;98: 1-8.	Case report
Tuttelmann F, Ivanov P, Dietzel C, Sofroniou A, Tsvyatkovska TM, Komsa-Penkova RS, Markoff A, Wieacker P, Bogdanova N. Further insights into the role of the annexin A5 M2 haplotype as recurrent pregnancy loss factor, assessing timing of miscarriage and partner risk. Fertility and sterility 2013;100: 1321-1325.	Genetic study
Vansenne F, Goddijn M, Redeker B, Snijder S, Gerssen-Schoorl K, Lemmink H, Leschot NJ, van der Veen F, Bossuyt PM, de Borgie CA. Knowledge and perceived risks in couples undergoing genetic testing after recurrent miscarriage or for poor semen quality. Reproductive biomedicine online 2011;23: 525-533.	Not relevant
Venkatesh S, Singh A, Shamsi MB, Thilagavathi J, Kumar R, Mitra DK, Dada R. Clinical significance of sperm DNA damage threshold value in the assessment of male infertility. Reproductive sciences (Thousand Oaks, Calif) 2011;18: 1005-1013.	Not RPL
Venkatesh S, Thilagavathi J, Kumar K, Deka D, Talwar P, Dada R. Cytogenetic, Y chromosome microdeletion, sperm chromatin and oxidative stress analysis in male partners of couples experiencing recurrent spontaneous abortions. Archives of gynecology and obstetrics 2011;284: 1577-1584.	Comparison of RPL with normal and abnormal sperm
Wang Z, Wang P, Wang X, He X, Wang Z, Xu D, Hu J, Wang B. Significant association between angiotensin-converting enzyme gene insertion/deletion polymorphism and risk of recurrent miscarriage: a systematic review and meta-analysis. Metabolism: clinical and experimental 2013;62: 1227-1238.	Genetic study
Worrilow KC, Eid S, Woodhouse D, Perloe M, Smith S, Witmyer J, Ivani K, Khoury C, Ball GD, Elliot T et al. Use of hyaluronan in the selection of sperm for intracytoplasmic sperm injection (ICSI): significant improvement in clinical outcomes--multicenter, double-blinded and randomized controlled trial Human reproduction . 2013, pp. 306-314.	Not RPL (ICSI)
Yang C, Fangfang W, Jie L, Yanlong Y, Jie W, Xuefei L, Xuerong Z, Yanling H. Angiotensin-converting enzyme insertion/deletion (I/D) polymorphisms and	Genetic study

recurrent pregnancy loss: a meta-analysis. Journal of assisted reproduction and genetics 2012;29: 1167-1173.	
Zini A. Are sperm chromatin and DNA defects relevant in the clinic? Systems biology in reproductive medicine 2011;57: 78-85.	Not RPL (IVF-ICSI)

10. WHICH THERAPEUTIC INTERVENTIONS SHOULD BE OFFERED TO PATIENTS WITH RPL DUE TO GENETIC/CHROMOSOMAL CAUSES TO INCREASE LIVE BIRTH RATE?

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Abuelo DN, Barsel-Bowers G. Prognosis for couples who have experienced repeated pregnancy loss. Fertility and sterility 1983;40: 844-845.	Old paper
Ambroggio J, Gindoff PR, Dayal MB, Khaldi R, Peak D, Frankfurter D, Dubey AK. Multinucleation of a sibling blastomere on day 2 suggests unsuitability for embryo transfer in IVF-preimplantation genetic screening cycles. Fertility and sterility 2011;96: 856-859.	Patients have RIF or RPL
Angiolucci M, Murru R, Melis G, Carcassi C, Mais V. Association between different morphological types and abnormal karyotypes in early pregnancy loss. Ultrasound in obstetrics & gynecology 2011;37: 219-225.	Not treatment
Audibert F, Wilson RD, Allen V, Blight C, Brock JA, Desilets VA, Gagnon A, Johnson JA, Langlois S, Wyatt P. Preimplantation genetic testing. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 2009;31: 761-775.	consensus of the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada
Balasch J, Creus M, Fabregues F, Civico S, Carmona F, Martorell J, Vanrell JA. In-vitro fertilization treatment for unexplained recurrent abortion: a pilot study. Human reproduction 1996;11: 1579-1582.	Small study – 3 or 4 embryos transferred (not current practice)
Bar-Ami S, Seibel MM, Pierce KE, Zilberstein M. Preimplantation genetic diagnosis for a couple with recurrent pregnancy loss and triploidy. Birth defects research Part A, Clinical and molecular teratology 2003;67: 946-950.	Case report
Baruch S, Kaufman DJ, Hudson KL. Preimplantation genetic screening: a survey of in vitro fertilization clinics. Genetics in medicine : official journal of the American College of Medical Genetics 2008;10: 685-690.	PGD in RM - clinical practice survey
Benzacken B, Carbillon L, Dupont C, Siffroi JP, Monier-Gavelle F, Bucourt M, Uzan M, Wolf JP. Lack of submicroscopic rearrangements involving	technical aspects, no clinical relevance

telomeres in reproductive failures. Human reproduction 2002;17: 1154-1157.	
Carp HJ, Dirnfeld M, Dor J, Grudzinskas JG. ART in recurrent miscarriage: preimplantation genetic diagnosis/screening or surrogacy? Human reproduction 2004;19: 1502-1505.	Included in review Franssen 2011
Chen CK, Wu D, Yu HT, Lin CY, Wang ML, Yeh HY, Huang HY, Wang HS, Soong YK, Lee CL. Preimplantation genetic diagnosis by fluorescence in situ hybridization of reciprocal and Robertsonian translocations. Taiwanese journal of obstetrics & gynecology 2014;53: 48-52.	No comparison
Clark DA, Daya S, Coulam CB, Gunby J. Implication of abnormal human trophoblast karyotype for the evidence-based approach to the understanding, investigation, and treatment of recurrent spontaneous abortion. The Recurrent Miscarriage Immunotherapy Trialists Group. American journal of reproductive immunology 1996;35: 495-498.	Editorial
Combelles CM, Kearns WG, Fox JH, Racowsky C. Cellular and genetic analysis of oocytes and embryos in a human case of spontaneous oocyte activation. Human reproduction 2011;26: 545-552.	case report
De Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. Human reproduction 1990;5: 519-528.	Not relevant, Prevalence of different genetic causes
Drugan A, Koppitch FC, 3rd, Williams JC, 3rd, Johnson MP, Moghissi KS, Evans MI. Prenatal genetic diagnosis following recurrent early pregnancy loss. Obstetrics and gynecology 1990;75: 381-384.	Old paper - Prenatal genetic diagnosis
Engels H, Eggermann T, Caliebe A, Jelska A, Schubert R, Schuler HM, Panasiuk B, Zaremba J, Latos-Bielenska A, Jakubowski L et al. Genetic counseling in Robertsonian translocations der(13;14): frequencies of reproductive outcomes and infertility in 101 pedigrees. American journal of medical genetics Part A 2008;146a: 2611-2616.	Not RPL
Findikli N, Kahraman S, Saglam Y, Beyazyurek C, Sertyel S, Karlikaya G, Karagozoglu H, Aygun B. Embryo aneuploidy screening for repeated implantation failure and unexplained recurrent miscarriage. Reproductive biomedicine online 2006;13: 38-46.	Literature review, not treatment
Fischer J, Colls P, Escudero T, Munne S. Preimplantation genetic diagnosis (PGD) improves pregnancy outcome for translocation carriers with a history of recurrent losses. Fertility and sterility 2010;94: 283-289.	Excluded in review Hirshfeld-Cytron; carriers could not be differentiated
Fortuny A, Carrio A, Soler A, Cararach J, Fuster J, Salami C. Detection of balanced chromosome rearrangements in 445 couples with repeated abortion and cytogenetic prenatal testing in carriers. Fertility and sterility 1988;49: 774-779.	Old paper
Franssen MT, Korevaar JC, Tjoa WM, Leschot NJ, Bossuyt PM, Knegt AC, Suykerbuyk RF, Hochstenbach R, van der Veen F, Goddijn M. Inherited unbalanced structural chromosome abnormalities at prenatal chromosome analysis are rarely ascertained through recurrent miscarriage. Prenatal diagnosis 2008;28: 408-411.	Unacceptable quality
Franssen MT, Korevaar JC, van der Veen F, Leschot NJ, Bossuyt PM, Goddijn M. Reproductive outcome after chromosome analysis in couples with two or more miscarriages: index [corrected]-control study. BMJ (Clinical research ed) 2006;332: 759-763.	Included in review Franssen 2011
Garrisi JG, Colls P, Ferry KM, Zheng X, Garrisi MG, Munne S. Effect of infertility, maternal age, and number of previous miscarriages on the outcome of preimplantation genetic diagnosis for idiopathic recurrent pregnancy loss. Fertility and sterility 2009;92: 288-295.	Excluded in review Musters 2011 due to no data extraction possible
Gianaroli L, Magli MC, Ferraretti AP, Tabanelli C, Trombetta C, Boudjema E. The role of preimplantation diagnosis for aneuploidies. Reproductive biomedicine online 2002;4 Suppl 3: 31-36.	Infertility – not RPL
Heinig J, Steinhard J, Schmitz R, Nofer JR, Kiesel L, Klockenbusch W. Maternal serum free beta-hCG and PAPP-A in patients with habitual abortion-influence on first-trimester screening for chromosomal abnormalities. Prenatal diagnosis 2007;27: 814-816.	Not relevant (serum free hCG)
Hirshfeld-Cytron J, Sugiura-Ogasawara M, Stephenson MD. Management of recurrent pregnancy loss associated with a parental carrier of a reciprocal translocation: a systematic review. Seminars in reproductive medicine 2011;29: 470-481.	Unacceptable quality

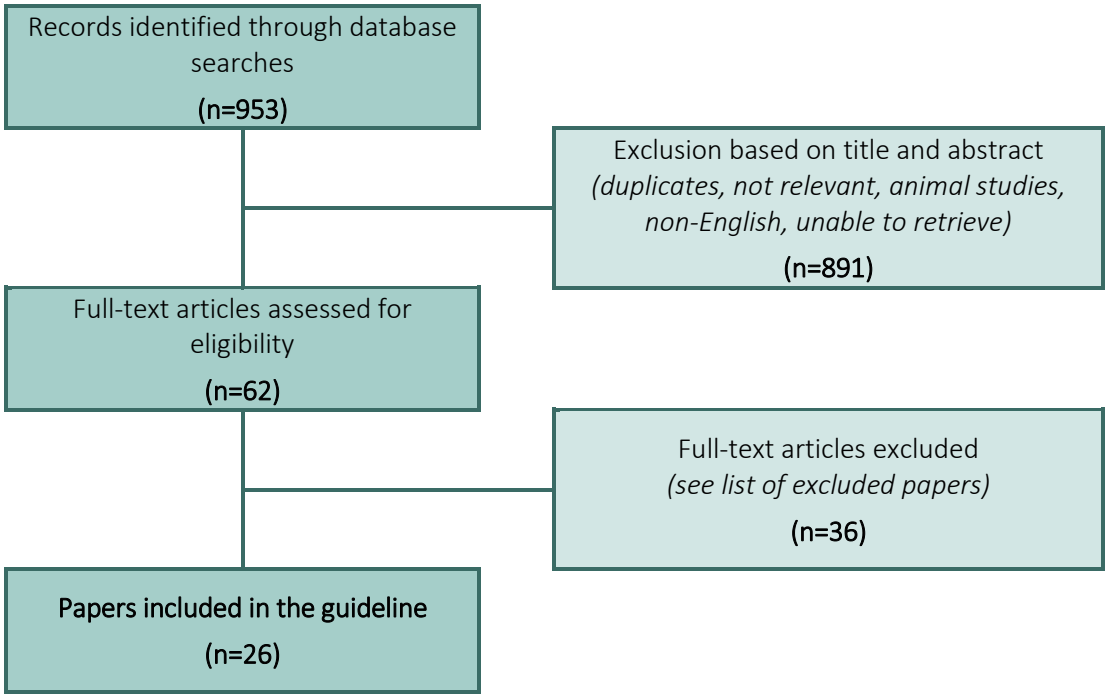
Hodes-Wertz B, Grifo J, Ghadir S, Kaplan B, Laskin CA, Glassner M, Munne S. Idiopathic recurrent miscarriage is caused mostly by aneuploid embryos. Fertility and sterility 2012;98: 675-680.	No comparison
Hsu WT, Shchepin DA, Mao R, Berry-Kravis E, Garber AP, Fischel-Ghodsian N, Falk RE, Carlson DE, Roeder ER, Leeth EA et al. Mosaic trisomy 16 ascertained through amniocentesis: evaluation of 11 new cases. American journal of medical genetics 1998;80: 473-480.	Technical paper – not RPL
Kahraman S, Benkhalifa M, Donmez E, Biricik A, Sertyel S, Findikli N, Berkil H. The results of aneuploidy screening in 276 couples undergoing assisted reproductive techniques. Prenatal diagnosis 2004;24: 307-311.	Diagnosis
Keymolen K, Staessen C, Verpoest W, Michiels A, Bonduelle M, Haentjens P, Vanderelst J, Liebaers I. A proposal for reproductive counselling in carriers of Robertsonian translocations: 10 years of experience with preimplantation genetic diagnosis. Human reproduction 2009;24: 2365-2371.	Only 22% had RPL
Lalioti MD. Can preimplantation genetic diagnosis overcome recurrent pregnancy failure? Current opinion in obstetrics & gynecology 2008;20: 199-204.	non-systematic review
Laurino MY, Bennett RL, Saraiya DS, Baumeister L, Doyle DL, Leppig K, Pettersen B, Resta R, Shields L, Uhrich S et al. Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. Journal of genetic counseling 2005;14: 165-181.	Guideline
Liu J, Wang W, Sun X, Liu L, Jin H, Li M, Witz C, Williams D, Griffith J, Skorupski J et al. DNA microarray reveals that high proportions of human blastocysts from women of advanced maternal age are aneuploid and mosaic. Biology of reproduction 2012;87: 148.	Not RPL
Mantzouratou A, Mania A, Fragouli E, Xanthopoulou L, Tashkandi S, Fordham K, Ranieri DM, Doshi A, Nuttall S, Harper JC et al. Variable aneuploidy mechanisms in embryos from couples with poor reproductive histories undergoing preimplantation genetic screening. Human reproduction 2007;22: 1844-1853.	Included in review Musters 2011
Mathur N, Triplett L, Stephenson MD. Miscarriage chromosome testing: utility of comparative genomic hybridization with reflex microsatellite analysis in preserved miscarriage tissue. Fertility and sterility 2014;101: 1349-1352.	Technical paper
Munne S, Chen S, Fischer J, Colls P, Zheng X, Stevens J, Escudero T, Oter M, Schoolcraft B, Simpson JL et al. Preimplantation genetic diagnosis reduces pregnancy loss in women aged 35 years and older with a history of recurrent miscarriages. Fertility and sterility 2005;84: 331-335.	Included in review Musters 2011
Munne S, Gianaroli L, Tur-Kaspa I, Magli C, Sandalinas M, Grifo J, Cram D, Kahraman S, Verlinsky Y, Simpson JL. Substandard application of preimplantation genetic screening may interfere with its clinical success. Fertility and sterility 2007;88: 781-784.	Narrative critique of RCTs
Ogilvie CM, Braude P, Scriven PN. Successful pregnancy outcomes after preimplantation genetic diagnosis (PGD) for carriers of chromosome translocations. Human fertility (Cambridge, England) 2001;4: 168-171.	Review, more recent data available
Otani T, Roche M, Mizuike M, Colls P, Escudero T, Munne S. Preimplantation genetic diagnosis significantly improves the pregnancy outcome of translocation carriers with a history of recurrent miscarriage and unsuccessful pregnancies. Reproductive biomedicine online 2006;13: 869-874.	Included in review Franssen 2011
Pazarbasi A, Demirhan O, Turgut M, Guzel I, Tastemir D. Inheritance of a translocation between chromosomes 12 and 16 in a family with recurrent miscarriages and a newborn with Down syndrome carrying the same translocation. Genetic counseling (Geneva, Switzerland) 2008;19: 301-308.	Case report
Pellicer A, Rubio C, Vidal F, Minguez Y, Gimenez C, Egozcue J, Remohi J, Simon C. In vitro fertilization plus preimplantation genetic diagnosis in patients with recurrent miscarriage: an analysis of chromosome abnormalities in human preimplantation embryos. Fertility and sterility 1999;71: 1033-1039.	Small study

Phillips OP, Tharapel AT, Shulman LP, Simpson JL, Elias S. Segregation analysis and genetic counseling when both parents carry balanced chromosomal translocations. Fertility and sterility 1991;56: 646-652.	Case report
Platteau P, Staessen C, Michiels A, Van Steirteghem A, Liebaers I, Devroey P. Preimplantation genetic diagnosis for aneuploidy screening in patients with unexplained recurrent miscarriages. Fertility and sterility 2005;83: 393-397; quiz 525-396.	Included in review Musters 2011
Pourjafari B, Pour-Jafari H, Farimani M, Ghahramani S, Saleh EK. Genetic counseling in carriers of reciprocal translocations involving two autosomes. Indian journal of human genetics 2012;18: 250-253.	Case report
Remohi J, Gallardo E, Levy M, Valbuena D, de los Santos MJ, Simon C, Pellicer A. Oocyte donation in women with recurrent pregnancy loss. Human reproduction 1996;11: 2048-2051.	Small study (8 patients) – high FSH
Robberecht C, Pexsters A, Deprest J, Fryns JP, D'Hooghe T, Vermeesch JR. Cytogenetic and morphological analysis of early products of conception following hystero-embryoscopy from couples with recurrent pregnancy loss. Prenatal diagnosis 2012;32: 933-942.	Not treatment
Rubio C, Buendia P, Rodrigo L, Mercader A, Mateu E, Peinado V, Delgado A, Milan M, Mir P, Simon C et al. Prognostic factors for preimplantation genetic screening in repeated pregnancy loss. Reproductive biomedicine online 2009;18: 687-693.	Not treatment
Rubio C, Pehlivan T, Rodrigo L, Simon C, Remohi J, Pellicer A. Embryo aneuploidy screening for unexplained recurrent miscarriage: a minireview. American journal of reproductive immunology (New York, NY : 1989) 2005;53: 159-165.	Not treatment
Rubio C, Simon C, Vidal F, Rodrigo L, Pehlivan T, Remohi J, Pellicer A. Chromosomal abnormalities and embryo development in recurrent miscarriage couples. Human reproduction 2003;18: 182-188.	Not treatment
Somprasit C, Aguinaga M, Cisneros PL, Torsky S, Carson SA, Buster JE, Amato P, McAdoo SL, Simpson JL, Bischoff FZ. Paternal gonadal mosaicism detected in a couple with recurrent abortions undergoing PGD: FISH analysis of sperm nuclei proves valuable. Reproductive biomedicine online 2004;9: 225-230.	Not relevant
Stephenson MD. Parental translocations and need for preimplantation genetic diagnosis? Distorting effects of ascertainment bias and the need for information-rich families. Fertility and sterility 2008;90: 891-892; author reply 892-893.	Letter
Stephenson MD, Sierra S. Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. Human reproduction 2006;21: 1076-1082.	Included in review Franssen 2011
Sugiura-Ogasawara M, Aoki K, Fujii T, Fujita T, Kawaguchi R, Maruyama T, Ozawa N, Sugi T, Takeshita T, Saito S. Subsequent pregnancy outcomes in recurrent miscarriage patients with a paternal or maternal carrier of a structural chromosome rearrangement. Journal of human genetics 2008;53: 622-628.	Included in review Franssen 2011
Sugiura-Ogasawara M, Suzumori K. Can preimplantation genetic diagnosis improve success rates in recurrent aborters with translocations? Human reproduction 2005;20: 3267-3270.	More recent data available from review Franssen 2011
van Leeuwen M, Vansenne F, Korevaar JC, van der Veen F, Goddijn M, Mol BW. Economic analysis of chromosome testing in couples with recurrent miscarriage to prevent handicapped offspring. Human reproduction 2013;28: 1737-1742.	Economic analysis
Vansenne F, de Borgie CA, Korevaar JC, Franssen MT, Pajkrt E, Hansson KB, Leschot NJ, Bossuyt PM, van der Veen F, Goddijn M. Low uptake of prenatal diagnosis after established carrier status of a balanced structural chromosome abnormality in couples with recurrent miscarriage. Fertility and sterility 2010;94: 296-300.e291-293.	Compliance
Vansenne F, Goddijn M, Redeker B, Snijder S, Gerssen-Schoorl K, Lemmink H, Leschot NJ, van der Veen F, Bossuyt PM, de Borgie CA. Knowledge and perceived risks in couples undergoing genetic testing after recurrent miscarriage or for poor semen quality. Reproductive biomedicine online 2011;23: 525-533.	Not relevant – knowledge of couples

Vidal F, Gimenez C, Rubio C, Simon C, Pellicer A, Santalo J, Egozcue J. FISH preimplantation diagnosis of chromosome aneuploidy in recurrent pregnancy wastage. Journal of assisted reproduction and genetics 1998;15: 310-313.	3 cases
Wakui K, Tanemura M, Suzumori K, Hidaka E, Ishikawa M, Kubota T, Fukushima Y. Clinical applications of two-color telomeric fluorescence in situ hybridization for prenatal diagnosis: identification of chromosomal translocation in five families with recurrent miscarriages or a child with multiple congenital anomalies. Journal of human genetics 1999;44: 85-90.	Technical paper
Werlin LB, Rodi I, Decherney A, Marello E, Hill D, Munne S. Preimplantation genetic diagnosis (PGD) as a beneficial tool in women with recurrent pregnancy loss (RPL) and advanced maternal age (AMA) Fertility and sterility. 2004, pp. S241.	Small study
Wilding M, Forman R, Hogewind G, Di Matteo L, Zullo F, Cappiello F, Dale B. Preimplantation genetic diagnosis for the treatment of failed in vitro fertilization-embryo transfer and habitual abortion. Fertility and sterility 2004;81: 1302-1307.	Included in review Musters 2011
Wilton L. Preimplantation genetic diagnosis and chromosome analysis of blastomeres using comparative genomic hybridization. Human reproduction update 2005;11: 33-41.	Technical review
Yakin K, Urman B. What next for preimplantation genetic screening? A clinician's perspective. Human reproduction 2008;23: 1686-1690.	PGD - RM, paper discusses lack of evidence
Yuen BH, Livingston JE, Poland BJ, Wittmann BK, Sy L, Cannon W. Human chorionic gonadotropin, estradiol, progesterone, prolactin, and B-scan ultrasound monitoring of complications in early pregnancy. Obstetrics and gynecology 1981;57: 207-214.	Not treatment

11. WHICH THERAPEUTIC INTERVENTIONS SHOULD BE OFFERED TO PATIENTS WITH RPL DUE TO METABOLIC ABNORMALITIES OR HORMONAL ABNORMALITIES TO INCREASE LIVE BIRTH RATE?

Flowchart



List of excluded papers

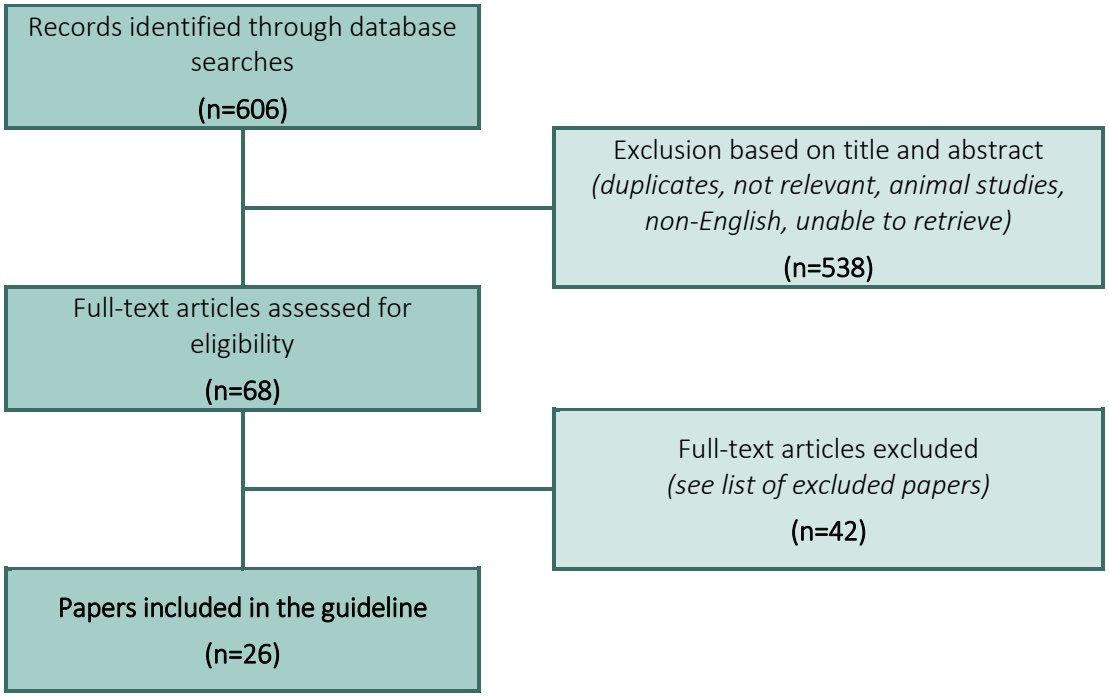
	EXCLUSION CRITERIA
Carp H. A systematic review of dydrogesterone for the treatment of recurrent miscarriage. Gynecological endocrinology 2015;31: 422-430.	Unexplained RM, more rece
Carp HJ. Recurrent miscarriage and hCG supplementation: a review and metaanalysis. Gynecological endocrinology 2010;26: 712-716.	Review included in UNEXPLAINED RPL
Carp HJ. Progestogens in the prevention of miscarriage. Hormone molecular biology and clinical investigation 2015.	Miscarriage, not RPL
Carpentier PA, Stanford JB, Boyle PC. Progesterone in Women with Recurrent Miscarriages. The New England journal of medicine 2016;374: 894.	Comment to Coomarasamy 2015
Check JH, Chase JS, Nowroozi K, Wu CH, Adelson HG. Progesterone therapy to decrease first-trimester spontaneous abortions in previous aborters. International journal of fertility 1987;32: 192-193, 197-199.	Old paper
Check JH, Lurie D, Davies E, Vetter B. Comparison of first trimester serum estradiol levels in aborters versus nonaborters during maintenance of normal progesterone levels. Gynecologic and obstetric investigation 1992;34: 206-210.	Not relevant
Check JH, Tarquini P, Gandy P, Lauer C. A randomized study comparing the efficacy of reducing the spontaneous abortion rate following lymphocyte immunotherapy and progesterone treatment versus progesterone alone in primary habitual aborters. Gynecologic and obstetric investigation 1995;39: 257-261.	Small study - lymphocyte immunotherapy and progesterone combination

Coomarasamy A, Williams H, Rai R. Progesterone in Women with Recurrent Miscarriages. The New England journal of medicine 2016;374: 894.	Author reply-study included in evidence table
Dante G, Vaccaro V, Facchinetti F. Use of progestagens during early pregnancy. Facts, views & vision in ObGyn 2013;5: 66-71.	Not RPL
El-Zibdeh MY. Dydrogesterone in the reduction of recurrent spontaneous abortion. The Journal of steroid biochemistry and molecular biology 2005;97: 431-434.	Included in review Haas 2013
Glueck CJ, Wang P, Goldenberg N, Sieve L. Pregnancy loss, polycystic ovary syndrome, thrombophilia, hypofibrinolysis, enoxaparin, metformin. Clinical and applied thrombosis/hemostasis 2004;10: 323-334.	PCOS patients with one or more previous PL, who also have thrombophilia and/or hypofibrinolysis
Haas DM, Ramsey PS. Progestogen for preventing miscarriage. The Cochrane database of systematic reviews 2013;10: Cd003511.	Discussed in Treatment for unexplained RPL
Harrison RF. Treatment of habitual abortion with human chorionic gonadotropin: results of open and placebo-controlled studies. European journal of obstetrics, gynecology, and reproductive biology 1985;20: 159-168.	Included in review Morley 2013
Harrison RF. Human chorionic gonadotrophin (hCG) in the management of recurrent abortion; results of a multi-centre placebo-controlled study. European journal of obstetrics, gynecology, and reproductive biology 1992;47: 175-179.	Included in review Morley 2013
Hekmatdoost A, Vahid F, Yari Z, Sadeghi M, Eini-Zinab H, Lakpour N, Arefi S. Methyltetrahydrofolate vs Folic Acid Supplementation in Idiopathic Recurrent Miscarriage with Respect to Methylenetetrahydrofolate Reductase C677T and A1298C Polymorphisms: A Randomized Controlled Trial. PloS one 2015;10: e0143569.	More relevant for thrombophilia treatment
Katz Z, Lancet M, Skornik J, Chemke J, Mogilner BM, Klinberg M. Teratogenicity of progestogens given during the first trimester of pregnancy. Obstetrics and gynecology 1985;65: 775-780.	Old paper
Kumar A, Begum N, Prasad S, Aggarwal S, Sharma S. Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial. Fertility and sterility 2014;102: 1357-1363.e1353.	Unexplained RM – discussed in chapter unexplained RPL
Li L, Dou L, Leung Ping C, Wang Chi C. Chinese herbal medicines for threatened miscarriage Cochrane Database of Systematic Reviews. 2012. John Wiley & Sons, Ltd.	Not RPL, no subanalysis
Nardo LG, Sallam HN. Progesterone supplementation to prevent recurrent miscarriage and to reduce implantation failure in assisted reproduction cycles. Reproductive biomedicine online 2006;13: 47-57.	Non-systematic review
Oates-Whitehead RM, Haas DM, Carrier JA. Progestogen for preventing miscarriage. The Cochrane database of systematic reviews 2003: Cd003511.	Older version of Haas 2013
Price M, Kelsberg G, Safranek S, Damitz B. Clinical inquiries. What treatments prevent miscarriage after recurrent pregnancy loss? The Journal of family practice 2005;54: 892, 894.	Describes the results of Oates-Whitehead 2003 for progesterone
Quenby S, Farquharson RG. Human chorionic gonadotropin supplementation in recurring pregnancy loss: a controlled trial. Fertility and sterility 1994;62: 708-710.	Included in review Morley 2013
Raghupathy R, Al Mutawa E, Makhseed M, Azizieh F, Szekeres-Bartho J. Modulation of cytokine production by dydrogesterone in lymphocytes from women with recurrent miscarriage. BJOG : an international journal of obstetrics and gynaecology 2005;112: 1096-1101.	Not a clinical study, no pregnancy related outcomes
Ragusa A, de Carolis C, dal Lago A, Miriello D, Ruggiero G, Brucato A, Pisoni MP, Muscara M, Merati R, Maccario L et al. Progesterone supplement in pregnancy: an immunologic therapy? Lupus 2004;13: 639-642.	Not relevant
Ramidi G, Khan N, Glueck CJ, Wang P, Goldenberg N. Enoxaparin-metformin and enoxaparin alone may safely reduce pregnancy loss. Translational research 2009;153: 33-43.	Women with PCOS, not RPL

Russu M, Stanculescu R, Nastasia S, Paun M, Mubarak N, Marin JA, Lachanas I. Pregnancy outcomes following preconception, early and late administration of vaginal micronized progesterone for recurrent pregnancy loss Ginecoro. 2009, pp. 10-15.	Small study - Folic Acid + vaginal micronized progesterone
Scott JR, Pattison N. Human chorionic gonadotrophin for recurrent miscarriage. The Cochrane database of systematic reviews 2000: Cd000101.	previous version of Morley 2013
Siklosi GS, Banhidy FG, Acs N. Fundamental role of folliculo-luteal function in recurrent miscarriage. Archives of gynecology and obstetrics 2012;286: 1299-1305.	Intervention (graduated clomiphene citrate) was not included in the PICO question
Stapley L. Treatment of luteal phase defect by ovarian stimulation. Trends in endocrinology and metabolism: TEM 2001;12: 146.	Reports on study Li 2001
Szekeres-Bartho J, Balasch J. Progestagen therapy for recurrent miscarriage. Human reproduction update 2008;14: 27-35.	Based on data of 3 old studies and 1 recent study – newer publications available
Szekeres-Bartho J, Wilczynski JR, Basta P, Kalinka J. Role of progesterone and progestin therapy in threatened abortion and preterm labour. Frontiers in bioscience 2008;13: 1981-1990.	Non-systematic review
Vissenberg R, Manders VD, Mastenbroek S, Fliers E, Afink GB, Ris-Stalpers C, Goddijn M, Bisschop PH. Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction. Human reproduction update 2015;21: 378-387.	Basic science, no data on RPL
Vissenberg R, van Dijk MM, Fliers E, van der Post JA, van Wely M, Bloemenkamp KW, Hoek A, Kuchenbecker WK, Verhoeve HR, Scheepers HCJ et al. Effect of levothyroxine on live birth rate in euthyroid women with recurrent miscarriage and TPO antibodies (T4-LIFE study). Contemporary clinical trials 2015.	Study protocol
Walch K, Hefler L, Nagele F. Oral dydrogesterone treatment during the first trimester of pregnancy: the prevention of miscarriage study (PROMIS). A double-blind, prospectively randomized, placebo-controlled, parallel group trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2005;18: 265-269.	Study protocol
Walch KT, Huber JC. Progesterone for recurrent miscarriage: truth and deceptions. Best practice & research Clinical obstetrics & gynaecology 2008;22: 375-389.	Non-systematic review
Yovich JL, Turner SR, Draper R. Medroxyprogesterone acetate therapy in early pregnancy has no apparent fetal effects. Teratology 1988;38: 135-144.	Old study – safety

12. WHICH THERAPEUTIC INTERVENTIONS SHOULD BE OFFERED TO PATIENTS WITH RPL DUE TO UTERINE ABNORMALITIES TO INCREASE LIVE BIRTH RATE?

Flowchart



List of excluded papers

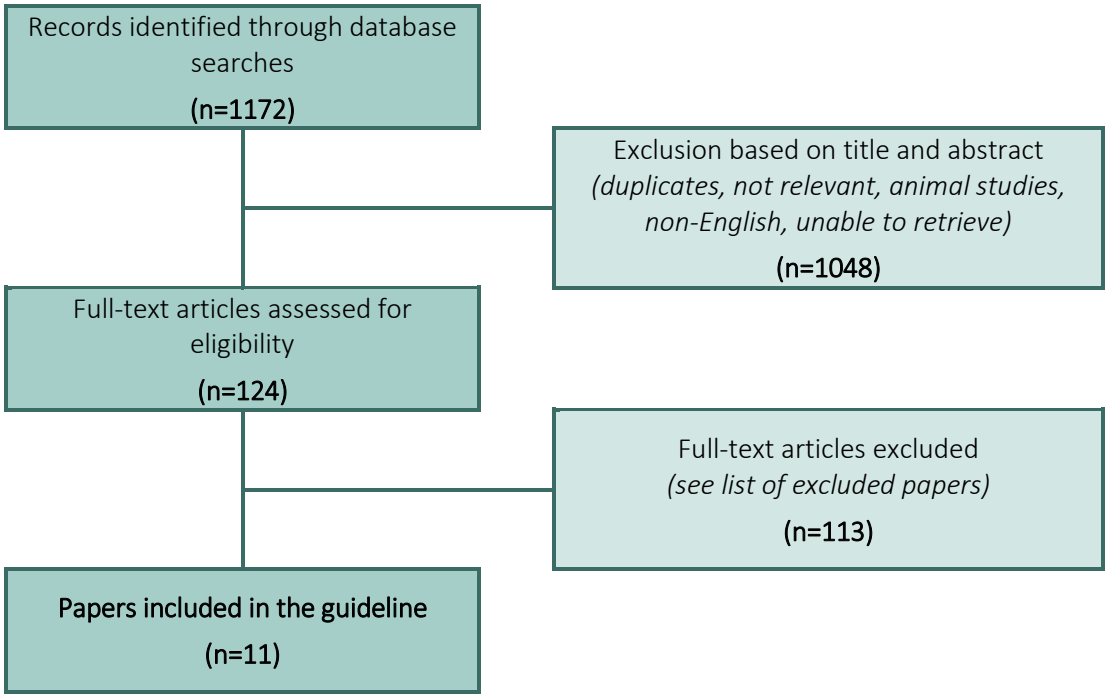
	EXCLUSION CRITERIA
Ayhan A, Yucel I, Tuncer ZS, Kisnisci HA. Reproductive performance after conventional metroplasty: an evaluation of 102 cases. Fertility and sterility 1992;57: 1194-1196.	Old and techniques not currently used
Barranger E, Gervaise A, Doumerc S, Fernandez H. Reproductive performance after hysteroscopic metroplasty in the hypoplastic uterus: a study of 29 cases. BJOG : an international journal of obstetrics and gynaecology 2002;109: 1331-1334.	Old – low number of patients
Bendifallah S, Faivre E, Legendre G, Deffieux X, Fernandez H. Metroplasty for AFS Class V and VI septate uterus in patients with infertility or miscarriage: reproductive outcomes study. J Minim Invasive Gynecol 2013;20: 178-184.	Not all RPL
Bosteels J, Weyers S, Puttemans P, Panayotidis C, Van Herendael B, Gomel V, Mol BW, Mathieu C, D'Hooghe T. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review. Human reproduction update 2010;16: 1-11.	Not all RPL, subfertile women
Brinsden PR. Gestational surrogacy. Human reproduction update 2003;9: 483-491.	Not RPL - surrogacy
Bulletti C, Flamigni C, Giacomucci E. Reproductive failure due to spontaneous abortion and recurrent miscarriage. Human reproduction update 1996;2: 118-136.	broad review on RIF and spontaneous abortion
Caliskan E, Ozkan S, Cakiroglu Y, Sarisoy HT, Corakci A, Ozeren S. Diagnostic accuracy of real-time 3D sonography in the diagnosis of congenital Mullerian	diagnosis

anomalies in high-risk patients with respect to the phase of the menstrual cycle. Journal of clinical ultrasound : JCU 2010;38: 123-127.	
Carp HJ, Dirnfeld M, Dor J, Grudzinskas JG. ART in recurrent miscarriage: preimplantation genetic diagnosis/screening or surrogacy? Human reproduction 2004;19: 1502-1505.	Opinion paper
Dib C, Araoz PA, Davies NP, Dearani JA, Ammash NM. Hypoplastic right-heart syndrome presenting as multiple miscarriages. Texas Heart Institute journal / from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital 2012;39: 249-254.	Case report
Doridot V, Gervaise A, Taylor S, Frydman R, Fernandez H. Obstetric outcome after endoscopic transection of the uterine septum. The Journal of the American Association of Gynecologic Laparoscopists 2003;10: 271-275.	Not all RPL
Fernandez H, Garbin O, Castaigne V, Gervaise A, Levaillant JM. Surgical approach to and reproductive outcome after surgical correction of a T-shaped uterus. Human reproduction 2011;26: 1730-1734.	Not all RPL
Garbin O, Ohl J, Bettahar-Lebugle K, Dellenbach P. Hysteroscopic metroplasty in diethylstilboestrol-exposed and hypoplastic uterus: a report on 24 cases. Human reproduction 1998;13: 2751-2755.	Low number of cases
Golan A, Langer R, Wexler S, Segev E, Niv D, David MP. Cervical cerclage--its role in the pregnant anomalous uterus. International journal of fertility 1990;35: 164-170.	Old – low number of cases
Goldberg JM, Falcone T, Attaran M. Sonohysterographic evaluation of uterine abnormalities noted on hysterosalpingography. Human reproduction 1997;12: 2151-2153.	Diagnosis
Gopal M, Goldberg J, Klein TA, Fossum GT. Embolization of a uterine arteriovenous malformation followed by a twin pregnancy. Obstetrics and gynecology 2003;102: 696-698.	Diagnosis
Grimbizis G, Camus M, Clasen K, Tournaye H, De Munck L, Devroey P. Hysteroscopic septum resection in patients with recurrent abortions or infertility. Human reproduction 1998;13: 1188-1193.	Included in review Valle 2013
Heinonen PK. Reproductive performance of women with uterine anomalies after abdominal or hysteroscopic metroplasty or no surgical treatment. The Journal of the American Association of Gynecologic Laparoscopists 1997;4: 311-317.	Not RPL patients
Hollett-Caines J, Vilos GA, Abu-Rafea B, Ahmad R. Fertility and pregnancy outcomes following hysteroscopic septum division. Journal of obstetrics and gynaecology Canada 2006;28: 156-159.	Not all RPL
Karande VC, Gleicher N. Resection of uterine septum using gynaecoradiological techniques. Human reproduction 1999;14: 1226-1229.	Not all RPL – small number of patients with RPL
Kerimis P, Zolti M, Sinwany G, Mashiach S, Carp H. Uterine rupture after hysteroscopic resection of uterine septum. Fertility and sterility 2002;77: 618-620.	Case report
Liddell HS, Lo C. Laparoscopic cervical cerclage: a series in women with a history of second trimester miscarriage. J Minim Invasive Gynecol 2008;15: 342-345.	Low number of cases
Ludwin A, Ludwin I, Banas T, Knafel A, Miedzyblocki M, Basta A. Diagnostic accuracy of sonohysterography, hysterosalpingography and diagnostic hysteroscopy in diagnosis of arcuate, septate and bicornuate uterus. The journal of obstetrics and gynaecology research 2011;37: 178-186.	Diagnosis
March CM, Israel R. Hysteroscopic management of recurrent abortion caused by septate uterus. American journal of obstetrics and gynecology 1987;156: 834-842.	Old
March CM, Israel R, March AD. Hysteroscopic management of intrauterine adhesions. American journal of obstetrics and gynecology 1978;130: 653-657.	Old – not RPL
Meresman GF, Olivares C, Vighi S, Alfie M, Irigoyen M, Etchepareborda JJ. Apoptosis is increased and cell proliferation is decreased in out-of-phase endometria from infertile and recurrent abortion patients. Reproductive biology and endocrinology : RB&E 2010;8: 126.	Diagnosis
Nagel TC, Malo JW. Hysteroscopic metroplasty in the diethylstilbestrol-exposed uterus and similar nonfusion anomalies: effects on subsequent	Not RPL

reproductive performance; a preliminary report. Fertility and sterility 1993;59: 502-506.	
Paradisi R, Barzanti R, Natali F, Battaglia C, Venturoli S. Metroplasty in a large population of women with septate uterus. J Minim Invasive Gynecol 2011;18: 449-454.	Not RPL
Pelosi MA. Laparoscopic Assisted Vaginal Metroplasty. The Journal of the American Association of Gynecologic Laparoscopists 1994;1: S28.	Technical report
Plouffe L, Jr., White EW, Tho SP, Sweet CS, Layman LC, Whitman GF, McDonough PG. Etiologic factors of recurrent abortion and subsequent reproductive performance of couples: have we made any progress in the past 10 years? American journal of obstetrics and gynecology 1992;167: 313-320; discussion 320-311.	Not relevant for question
Raziel A, Friedler S, Schachter M, Strassburger D, Ron-El R. Successful pregnancy after 24 consecutive fetal losses: lessons learned from surrogacy. Fertility and sterility 2000;74: 104-106.	Case report
Raziel A, Schachter M, Strassburger D, Komarovsky D, Ron-El R, Friedler S. Eight years' experience with an IVF surrogate gestational pregnancy programme. Reproductive biomedicine online 2005;11: 254-258.	Not RPL specific - surrogacy
Roy KK, Singla S, Baruah J, Kumar S, Sharma JB, Karmakar D. Reproductive outcome following hysteroscopic septal resection in patients with infertility and recurrent abortions. Archives of gynecology and obstetrics 2011;283: 273-279.	Not all RPL
Saravelos SH, Cocksedge KA, Li TC. Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: a critical appraisal. Human reproduction update 2008;14: 415-429.	Diagnosis
Saravelos SH, Cocksedge KA, Li TC. The pattern of pregnancy loss in women with congenital uterine anomalies and recurrent miscarriage. Reproductive biomedicine online 2010;20: 416-422.	Not treatment
Shahrokh Tehraninejad E, Ghaffari F, Jahangiri N, Oroomiechiha M, Akhoond MR, Aziminekoo E. Reproductive Outcome following Hysteroscopic Monopolar Metroplasty: An Analysis of 203 Cases. International journal of fertility & sterility 2013;7: 175-180.	Not all patients had RPL
Shawki HE. Reproductive outcomes after Versapoint hysteroscopic metroplasty Middle East Fertility Society Journal. 2010, pp. 259-264.	Only 11 women with RPL
Sills ES, Healy CM. Building Irish families through surrogacy: medical and judicial issues for the advanced reproductive technologies. Reproductive health 2008;5: 9.	Not treatment
Stein AL, March CM. Pregnancy outcome in women with mullerian duct anomalies. The Journal of reproductive medicine 1990;35: 411-414.	Not RPL
Sugiura-Ogasawara M, Ozaki Y, Kitaori T, Kumagai K, Suzuki S. Midline uterine defect size is correlated with miscarriage of euploid embryos in recurrent cases. Fertility and sterility 2010;93: 1983-1988.	Not treatment
Tofoski G, Dimitrov G, Georgievska J, Aluloski I, Gruevski K. Reproductive outcome after hysteroscopic metroplasty in patients with infertility and recurrent pregnancy loss. Prilozi / Makedonska akademija na naukite i umetnostite, Oddelenie za bioloski i medicinski nauki = Contributions / Macedonian Academy of Sciences and Arts, Section of Biological and Medical Sciences 2011;32: 141-154.	Only subgroup had RPL
Valle RF, Sciarra JJ. Hysteroscopic treatment of the septate uterus. Obstetrics and gynecology 1986;67: 253-257.	Included in review Valle 2013
Valli E, Zupi E, Marconi D, Vaquero E, Giovannini P, Lazzarin N, Romanini C. Hysteroscopic findings in 344 women with recurrent spontaneous abortion. The Journal of the American Association of Gynecologic Laparoscopists 2001;8: 398-401.	diagnosis, not treatment

13. WHICH THERAPEUTIC INTERVENTIONS SHOULD BE OFFERED TO PATIENTS WITH RPL DUE TO THROMBOPHILIA + ANTIPHOSPHOLIPID SYNDROME TO INCREASE LIVE BIRTH RATE?

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Arachchillage DR, Machin SJ, Mackie IJ, Cohen H. Diagnosis and management of non-criteria obstetric antiphospholipid syndrome. Thrombosis and haemostasis 2015;113: 13-19.	Included in diagnosis chapter
Bain E, Wilson A, Tooher R, Gates S, Davis L-J, Middleton P. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period Cochrane Database of Systematic Reviews. 2014.	Not miscarriage
Bick RL, Hoppensteadt D. Recurrent miscarriage syndrome and infertility due to blood coagulation protein/platelet defects: a review and update. Clinical and applied thrombosis/hemostasis 2005;11: 1-13.	Non-systematic review
Bladt V, Steengaard-Pedersen K, Poulsen LH, Petersen OB, Laursen B, d'Amore F. Late puerperal thrombohemorrhagic complications in a patient with antiphospholipid syndrome. European journal of haematology 2004;73: 437-440.	Case report
Boas WV, Goncalves RO, Costa OL, Goncalves MS. Metabolism and gene polymorphisms of the folate pathway in Brazilian women with history of recurrent abortion. Revista brasileira de ginecologia e obstetricia 2015;37: 71-76.	Not treatment
Bouvier S, Cochery-Nouvellon E, Lavigne-Lissalde G, Mercier E, Fabbro-Peray P, Balducchi JP, Mares P, Gris JC. Comparative incidence of pregnancy outcomes in thrombophilia-positive women from the NOH-APS observational study. Blood 2014;123: 414-421.	No comparison of treated versus non-treated patients

Bouvier S, Cochery-Nouvellon E, Lavigne-Lissalde G, Mercier E, Marchetti T, Balducchi JP, Mares P, Gris JC. Comparative incidence of pregnancy outcomes in treated obstetric antiphospholipid syndrome: the NOH-APS observational study. Blood 2014;123: 404-413.	Included in diagnosis chapter
Brenner B. Antithrombotic prophylaxis for women with thrombophilia and pregnancy complications--Yes. Journal of thrombosis and haemostasis : JTH 2003;1: 2070-2072.	Expert opinion
Brenner B. Maternal anticoagulant prophylaxis for prevention of pregnancy loss in women with thrombophilia. Journal of thrombosis and haemostasis : JTH 2003;1: 416-417.	Commentary
Buckingham KL, Chamley LW. A critical assessment of the role of antiphospholipid antibodies in infertility. Journal of reproductive immunology 2009;80: 132-145.	Infertility
Carp HJ, Sapir T, Shoenfeld Y. Intravenous immunoglobulin and recurrent pregnancy loss. Clinical reviews in allergy & immunology 2005;29: 327-332.	Non-systematic review
Carreras LD, Perez GN, Vega HR, Casavilla F. Lupus anticoagulant and recurrent fetal loss: successful treatment with gammaglobulin. Lancet 1988;2: 393-394.	Outdated
Check JH. The use of heparin for preventing miscarriage. American journal of reproductive immunology 2012;67: 326-333.	Non-systematic review
Christiansen OB. Treatment of pregnant women with recurrent miscarriage associated with phospholipid antibodies. General prognosis is favourable in untreated women. BMJ 1997;315: 372; author reply 373.	Author reply
Christiansen OB. Intravenous immunoglobulin in the prevention of recurrent spontaneous abortion: the European experience. American journal of reproductive immunology 1998;39: 77-81.	Review of 2005 available on the topic
Christiansen OB. Advances of intravenous immunoglobulin G in modulation of anti-fetal immunity in selected at-risk populations: science and therapeutics. Clinical and experimental immunology 2014;178 Suppl 1: 120-122.	Basic science study
Clark DA, Coulam CB, Stricker RB. Is intravenous immunoglobulins (IVIG) efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail in vitro fertilization and embryo transfer (IVF). Journal of assisted reproduction and genetics 2006;23: 1-13.	Not RPL
Clark DA, Gunby J, Daya S. The use of allogeneic leukocytes or i.v. IgG for the treatment of patients with recurrent spontaneous abortions. Transfusion medicine reviews 1997;11: 85-94.	Old review IVIG, more recent review available
Clifford K, Rai R, Watson H, Franks S, Regan L. Does suppressing luteinising hormone secretion reduce the miscarriage rate? Results of a randomised controlled trial. BMJ 1996;312: 1508-1511.	Patient population not appropriate for this question
Cohn DM, Goddijn M, Middeldorp S, Korevaar JC, Dawood F, Farquharson RG. Recurrent miscarriage and antiphospholipid antibodies: prognosis of subsequent pregnancy. Journal of thrombosis and haemostasis : JTH 2010;8: 2208-2213.	Cohort study, RCTs and reviews available
Coloma Bazan E, Donate Lopez C, Moreno Lozano P, Cervera R, Espinosa G. Discontinuation of anticoagulation or antiaggregation treatment may be safe in patients with primary antiphospholipid syndrome when antiphospholipid antibodies became persistently negative. Immunologic research 2013;56: 358-361.	Not RPL
Coppens M, Folkeringa N, Teune MJ, Hamulyak K, van der Meer J, Prins MH, Buller HR, Middeldorp S. Outcome of the subsequent pregnancy after a first loss in women with the factor V Leiden or prothrombin 20210A mutations. Journal of thrombosis and haemostasis : JTH 2007;5: 1444-1448.	Pregnancy outcome without treatment, not all RM patients
Coulam CB, Stern JJ, Bustillo M. Ultrasonographic findings of pregnancy losses after treatment for recurrent pregnancy loss: intravenous immunoglobulin versus placebo. Fertility and sterility 1994;61: 248-251.	Not focused on thrombophilia
Dante G, Vaccaro V, Facchinetti F. Use of progestagens during early pregnancy. Facts, views & vision in ObGyn 2013;5: 66-71.	Review based on Cochrane reviews

Daya S, Gunby J, Clark DA. Intravenous immunoglobulin therapy for recurrent spontaneous abortion: a meta-analysis. American journal of reproductive immunology 1998;39: 69-76.	Not RPL associated with thrombophilia
de Jesus GR, Rodrigues G, de Jesus NR, Levy RA. Pregnancy morbidity in antiphospholipid syndrome: what is the impact of treatment? Current rheumatology reports 2014;16: 403.	Non-systematic review
de Jong PG, Goddijn M, Middeldorp S. Antithrombotic therapy for pregnancy loss. Human reproduction update 2013;19: 656-673.	More recent review of the same author available
de Jong PG, Quenby S, Bloemenkamp KW, Braams-Lisman BA, de Bruin JP, Coomarasamy A, David M, DeSancho MT, van der Heijden OW, Hoek A et al. ALIFE2 study: low-molecular-weight heparin for women with recurrent miscarriage and inherited thrombophilia--study protocol for a randomized controlled trial. Trials 2015;16: 208.	Study protocol
Deligiannidis A, Parapanissiou E, Mavridis P, Tabakoudis G, Mavroudi A, Papastavrou T, Tabakoudis P. Thrombophilia and antithrombotic therapy in women with recurrent spontaneous abortions. The Journal of reproductive medicine 2007;52: 499-502.	Case control study of 52 women
Deligiannidis A, Parapanissiou E, Mavroudi A, Papastavrou T. Neonatal thrombocytopenia as side effect of immunotherapy for recurrent spontaneous abortion. American journal of reproductive immunology 2007;57: 167-168.	Case report
Dendrinos S, Sakkas E, Makrakis E. Low-molecular-weight heparin versus intravenous immunoglobulin for recurrent abortion associated with antiphospholipid antibody syndrome. International journal of gynaecology and obstetrics 2009;104: 223-225.	LMWH versus IVIG
Di Nisio M, Peters L, Middeldorp S. Anticoagulants for the treatment of recurrent pregnancy loss in women without antiphospholipid syndrome. The Cochrane database of systematic reviews 2005: Cd004734.	RPL without APS
D'Ippolito S, Ortiz AS, Veglia M, Tersigni C, Di Simone N. Low molecular weight heparin in obstetric care: a review of the literature. Reproductive sciences (Thousand Oaks, Calif) 2011;18: 602-613.	Obstretric care (mixed population)
Donohoe S, Quenby S, Mackie I, Panal G, Farquharson R, Malia R, Kingdom J, Machin S. Fluctuations in levels of antiphospholipid antibodies and increased coagulation activation markers in normal and heparin-treated antiphospholipid syndrome pregnancies. Lupus 2002;11: 11-20.	Measurement of coagulation markers and aPL in normal pregnancy and APS
Drewlo S. Heparin--not only thinning the blood. Blood 2013;121: 1932-1933.	Comment on a murine study on heparin
Egerup P, Lindschou J, Gluud C, Christiansen OB. The Effects of Intravenous Immunoglobulins in Women with Recurrent Miscarriages: A Systematic Review of Randomised Trials with Meta-Analyses and Trial Sequential Analyses Including Individual Patient Data. PloS one 2015;10: e0141588.	Not relevant for this question (included elsehere)
Eldor A. Unexplored territories in the nonsurgical patient: a look at pregnancy. Seminars in hematology 2001;38: 39-48.	Non-systematic review
El-Haieg DO, Zanati MF, El-Foual FM. Plasmapheresis and pregnancy outcome in patients with antiphospholipid syndrome. International journal of gynaecology and obstetrics 2007;99: 236-241.	No control group
Elmahashi MO, Elbareg AM, Essadi FM, Ashur BM, Adam I. Low dose aspirin and low-molecular-weight heparin in the treatment of pregnant Libyan women with recurrent miscarriage. BMC research notes 2014;7: 23.	RPL patients without thrombophilia
Erkan D, Patel S, Nuzzo M, Gerosa M, Meroni PL, Tincani A, Lockshin MD. Management of the controversial aspects of the antiphospholipid syndrome pregnancies: a guide for clinicians and researchers. Rheumatology 2008;47 Suppl 3: iii23-27.	Questionnaire on controversial aspects of aPL pos pregnancies
Ghosh K, Shetty S, Vora S, Salvi V. Successful pregnancy outcome in women with bad obstetric history and recurrent fetal loss due to thrombophilia: effect of unfractionated heparin and low-molecular weight heparin. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 2008;14: 174-179.	Small study (n=25)

Glueck CJ, Pranikoff J, Khan N, Riaz K, Chavan K, Raj P, Umar M, Wang P. High factor XI, recurrent pregnancy loss, enoxaparin. Fertility and sterility 2010;94: 2828-2831.	Case report of 3 cases
Glueck CJ, Wang P, Goldenberg N, Sieve L. Pregnancy loss, polycystic ovary syndrome, thrombophilia, hypofibrinolysis, enoxaparin, metformin. Clinical and applied thrombosis/hemostasis 2004;10: 323-334.	PCOS
Grandone E, De Stefano V, Rossi E, Cappucci F, Colaizzo D, Margaglione M. Antithrombotic prophylaxis during pregnancy in women with deficiency of natural anticoagulants. Blood coagulation & fibrinolysis 2008;19: 226-230.	Retrospective cohort study of 32 patients
Greer IA. Antithrombotic treatment for recurrent pregnancy loss? Journal of thrombosis and haemostasis : JTH 2011;9 Suppl 1: 302-305.	Non-systematic review
Greer IA, Brenner B, Gris JC. Antithrombotic treatment for pregnancy complications: which path for the journey to precision medicine? British journal of haematology 2014;165: 585-599.	Non-systematic review
Gris JC. LMWH have no place in recurrent pregnancy loss: debate-against the motion. Thrombosis research 2011;127 Suppl 3: S110-112.	Expert opinion
Gris JC, Mares P. The long and winding road ... towards LMWH for pregnancy loss. Journal of thrombosis and haemostasis : JTH 2005;3: 224-226.	Comment on Brenner 2005
Hauser AC, Hauser L, Pabinger-Fasching I, Quehenberger P, Derfler K, Horl WH. The course of anticardiolipin antibody levels under immunoadsorption therapy. American journal of kidney diseases 2005;46: 446-454.	SLE patients (small study)
Heine O, Mueller-Eckhardt G. Intravenous immune globulin in recurrent abortion. Clinical and experimental immunology 1994;97 Suppl 1: 39-42.	Non-systematic review
Hekmatdoost A, Vahid F, Yari Z, Sadeghi M, Eini-Zinab H, Lakpour N, Arefi S. Methyltetrahydrofolate vs Folic Acid Supplementation in Idiopathic Recurrent Miscarriage with Respect to Methylenetetrahydrofolate Reductase C677T and A1298C Polymorphisms: A Randomized Controlled Trial. PloS one 2015;10: e0143569.	RPL + MTHFR mutation
Hewell SW, Hammer RH. Antiphospholipid antibodies: a threat throughout pregnancy. Journal of obstetric, gynecologic, and neonatal nursing 1997;26: 162-168.	Non-systematic review
Hovdenak N, Haram K. Influence of mineral and vitamin supplements on pregnancy outcome. European journal of obstetrics, gynecology, and reproductive biology 2012;164: 127-132.	Non-systematic review – not miscarriage
Hutton B, Sharma R, Fergusson D, Tinmouth A, Hebert P, Jamieson J, Walker M. Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review. BJOG 2007;114: 134-142.	Older review
Jeremic K, Pervulov M, Gojnic M, Dukanac J, Ljubic A, Stojnic J. Comparison of two therapeutic protocols in patients with antiphospholipid antibodies and recurrent miscarriages. Vojnosanitetski pregled Military-medical and pharmaceutical review 2005;62: 435-439.	Cohort study of 40 patients
Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. The Cochrane database of systematic reviews 2009: Cd004734.	Older review on RPL without APS
Kalra S, Tuli A, Choudhry R, Raheja S. Prevalence of anticardiolipin antibody IgG in recurrent first trimester abortions and the role of aspirin in its prevention. Medical science monitor 2003;9: Cr213-216.	No control group
Katz Z, Lancet M, Skornik J, Chemke J, Mogilner BM, Klinberg M. Teratogenicity of progestogens given during the first trimester of pregnancy. Obstetrics and gynecology 1985;65: 775-780.	Old study on safety
Khalifeh A, Grantham J, Byrne J, Murphy K, McAuliffe F, Byrne B. Tinzaparin safety and efficacy in pregnancy. Irish journal of medical science 2014;183: 249-252.	Women with VTE or RPL
Kingdom J, Jauniaux E. Treatment of pregnant women with recurrent miscarriage associated with phospholipid antibodies. No cytogenetic data were reported. BMJ 1997;315: 372.	Letter to the editor

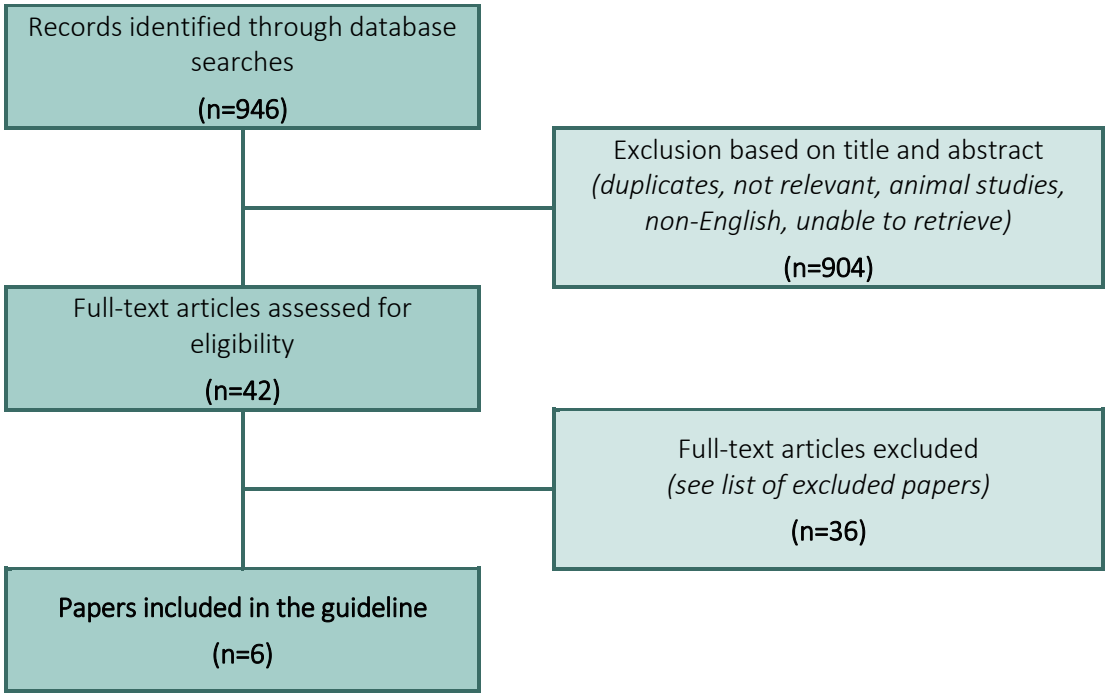
Kobayashi S, Tamura N, Tsuda H, Mokuno C, Hashimoto H, Hirose S. Immunoadsorbent plasmapheresis for a patient with antiphospholipid syndrome during pregnancy. Annals of the rheumatic diseases 1992;51: 399-401.	Old study, unclear relevance
Kosar A, Kasapoglu B, Kalyoncu S, Turan H, Balcik OS, Gumus EI. Treatment of adverse perinatal outcome in inherited thrombophilias: a clinical study. Blood coagulation & fibrinolysis 2011;22: 14-18.	prevalence mutations, outcome, some treated, but not compared to untreated
Krabbendam I, Dekker GA. Pregnancy outcome in patients with a history of recurrent spontaneous miscarriages and documented thrombophilias. Gynecologic and obstetric investigation 2004;57: 127-131.	No comparison of treatment
Kutteh WH. Antiphospholipid antibody syndrome and reproduction. Current opinion in obstetrics & gynecology 2014;26: 260-265.	Narrative review
Kwak-Kim J, Agcaoili MS, Aleta L, Liao A, Ota K, Dambaeva S, Beaman K, Kim JW, Gilman-Sachs A. Management of women with recurrent pregnancy losses and antiphospholipid antibody syndrome. American journal of reproductive immunology 2013;69: 596-607.	Non-systematic review
Levin BL, Varga E. MTHFR: Addressing Genetic Counseling Dilemmas Using Evidence-Based Literature. Journal of genetic counseling 2016.	Included in diagnosis chapter
Li L, Dou L, Leung Ping C, Wang Chi C. Chinese herbal medicines for threatened miscarriage Cochrane Database of Systematic Reviews. 2012.	Threatened miscarriage
Lim W. Antiphospholipid antibody syndrome. Hematology 2009: 233-239.	Non-systematic review
Lindqvist PG, Merlo J. Low molecular weight heparin for repeated pregnancy loss: is it based on solid evidence? Journal of thrombosis and haemostasis 2005;3: 221-223.	Comment to Brenner 2005
Lund M, Nielsen HS, Hviid TV, Steffensen R, Nyboe Andersen A, Christiansen OB. Hereditary thrombophilia and recurrent pregnancy loss: a retrospective cohort study of pregnancy outcome and obstetric complications. Human reproduction 2010;25: 2978-2984.	pregnancy outcome in women with RPL+ hereditary thrombophilia without treatment
Mekinian A, Loire-Berson P, Nicaise-Roland P, Lachassinne E, Stirnemann J, Boffa MC, Chollet-Martin S, Carbillon L, Fain O. Outcomes and treatment of obstetrical antiphospholipid syndrome in women with low antiphospholipid antibody levels. Journal of reproductive immunology 2012;94: 222-226.	Retrospective cohort study
Middeldorp S. Antithrombotic prophylaxis for women with thrombophilia and pregnancy complications--No. Journal of thrombosis and haemostasis 2003;1: 2073-2074.	Opinion paper
Middeldorp S. New studies of low-molecular-weight heparin in pregnancy. Thrombosis research 2015;135 Suppl 1: S26-29.	Non-systematic review
Misra D, Aledort L. Recurrent miscarriages: caution regarding development of clinical trials using low molecular weight heparin and pregnancy. American journal of hematology 2011;86: 235.	Anti Xa levels, not relevant
Mo D, Saravelos S, Metwally M, Makris M, Li TC. Treatment of recurrent miscarriage and antiphospholipid syndrome with low-dose enoxaparin and aspirin. Reproductive biomedicine online 2009;19: 216-220.	Pilot study for RCT
Monien S, Kadecki O, Baumgarten S, Salama A, Dorner T, Kiesewetter H. Use of heparin in women with early and late miscarriages with and without thrombophilia. Clinical and applied thrombosis/hemostasis 2009;15: 636-644.	Unexplained RPL
Mueller-Eckhardt G. Immunotherapy with intravenous immunoglobulin for prevention of recurrent pregnancy loss: European experience. American journal of reproductive immunology 1994;32: 281-285.	Older review including similar studies
Mumford SL, Silver RM, Sjaarda LA, Wactawski-Wende J, Townsend JM, Lynch AM, Galai N, Lesher LL, Faraggi D, Perkins NJ et al. Expanded findings from a randomized controlled trial of preconception low-dose aspirin and pregnancy loss. Human reproduction 2016;31: 657-665.	Not RPL or APS/thrombophilia
Nelen WL, Blom HJ, Steegers EA, den Heijer M, Thomas CM, Eskes TK. Homocysteine and folate levels as risk factors for recurrent early pregnancy loss. Obstetrics and gynecology 2000;95: 519-524.	Not treatment
Nielsen HS, Christiansen OB. Prognostic impact of anticardiolipin antibodies in women with recurrent miscarriage negative for the lupus anticoagulant. Human reproduction 2005;20: 1720-1728.	Not treatment

Opatrny L, David M, Kahn SR, Shrier I, Rey E. Association between antiphospholipid antibodies and recurrent fetal loss in women without autoimmune disease: a metaanalysis. The Journal of rheumatology 2006;33: 2214-2221.	Included in diagnosis chapter – not treatment
Ordi J, Barquinero J, Vilardell M, Jordana R, Tolosa C, Selva A, Genover E. Fetal loss treatment in patients with antiphospholipid antibodies. Annals of the rheumatic diseases 1989;48: 798-802.	To old, more recent studies available
Pagliaro P, Arrigoni L, Muggiasca ML, Poggio M, Russo U, Rossi E. Primary thrombocythemia and pregnancy: treatment and outcome in fifteen cases. American journal of hematology 1996;53: 6-10.	Not RPL
Pasquier E, de Saint Martin L, Le Gal G. Antithrombotic medications and recurrent miscarriage. The New England journal of medicine 2010;363: 887; author reply 888.	Author reply
Pelloux H, Fricker-Hidalgo H, Brochier G, Goullier-Fleuret A, Ambroise-Thomas P. Intravenous immunoglobulin therapy: confounding effects on serological screening for toxoplasmosis during pregnancy. Journal of clinical microbiology 1999;37: 3423-3424.	Case report
Pena RB, Cadavid AP, Botero JH, Garcia GP, Gallego MI, Ossa JE. The production of MLR-blocking factors after lymphocyte immunotherapy for RSA does not predict the outcome of pregnancy. American journal of reproductive immunology 1998;39: 120-124.	Not relevant for the key question
Piette JC, Huong DL, Wechsler B. Treatment of pregnant women with recurrent miscarriage associated with phospholipid antibodies. During pregnancy, heparin should be stopped during labour and then restarted soon after delivery. BMJ 1997;315: 372-373; author reply 373.	Author reply
Quere I, Mercier E, Bellet H, Janbon C, Mares P, Gris JC. Vitamin supplementation and pregnancy outcome in women with recurrent early pregnancy loss and hyperhomocysteinemia. Fertility and sterility 2001;75: 823-825.	Included for hyperhomocysteinemia
Rambaldi MP, Mecacci F, Guaschino S, Paidas MJ. Inherited and acquired thrombophilias. Reproductive sciences 2014;21: 167-182.	Non-systematic review
Ramidi G, Khan N, Glueck CJ, Wang P, Goldenberg N. Enoxaparin-metformin and enoxaparin alone may safely reduce pregnancy loss. Translational research 2009;153: 33-43.	PCOS
Ray JG, Laskin CA. Folic acid and homocyst(e)ine metabolic defects and the risk of placental abruption, pre-eclampsia and spontaneous pregnancy loss: A systematic review. Placenta 1999;20: 519-529.	Not treatment
Rodger MA, Paidas M, McLintock C, Middeldorp S, Kahn S, Martinelli I, Hague W, Rosene Montella K, Greer I. Inherited thrombophilia and pregnancy complications revisited. Obstetrics and gynecology 2008;112: 320-324.	commentary
Rogenhofer N, Bohlmann MK, Beuter-Winkler P, Wurfel W, Rank A, Thaler CJ, Toth B. Prevention, management and extent of adverse pregnancy outcomes in women with hereditary antithrombin deficiency. Annals of hematology 2014;93: 385-392.	Small study with 7 patients
Ronnenberg AG, Venners SA, Xu X, Chen C, Wang L, Guang W, Huang A, Wang X. Preconception B-vitamin and homocysteine status, conception, and early pregnancy loss. American journal of epidemiology 2007;166: 304-312.	Not treatment
Shimada S, Takeda M, Nishihira J, Kaneuchi M, Sakuragi N, Minakami H, Yamada H. A high dose of intravenous immunoglobulin increases CD94 expression on natural killer cells in women with recurrent spontaneous abortion. American journal of reproductive immunology 2009;62: 301-307.	Basic study on IVIG
Stern C, Chamley L. Antiphospholipid antibodies and coagulation defects in women with implantation failure after IVF and recurrent miscarriage. Reproductive biomedicine online 2006;13: 29-37.	Diagnosis, not treatment
Stricker RB, Steinleitner A, Bookoff CN, Weckstein LN, Winger EE. Successful treatment of immunologic abortion with low-dose intravenous immunoglobulin. Fertility and sterility 2000;73: 536-540.	Mixed patient group

Stricker RB, Winger EE. Update on treatment of immunologic abortion with low-dose intravenous immunoglobulin. American journal of reproductive immunology 2005;54: 390-396.	Not relevant for this question
Sugiura-Ogasawara M, Ozaki Y, Nakanishi T, Sato T, Suzumori N, Kumagai K. Occasional antiphospholipid antibody positive patients with recurrent pregnancy loss also merit aspirin therapy: a retrospective cohort-control study. American journal of reproductive immunology 2008;59: 235-241.	Occasional antiphospholipid antibodies
Takakuwa K, Ishii K, Takaki Y, Natsume N, Adachi H, Kurata H, Tamura M, Kurabayasi T, Tanaka K. Effect of sairei-to combined with aspirin and prednisolone on four recurrent reproductive failure women who are positive for anti-phospholipid antibodies. The American journal of Chinese medicine 2003;31: 659-663.	Case reports
Tan WK, Lim SK, Tan LK, Bauptista D. Does low-molecular-weight heparin improve live birth rates in pregnant women with thrombophilic disorders? A systematic review. Singapore medical journal 2012;53: 659-663.	Not RPL
Triolo G, Ferrante A, Accardo-Palumbo A, Ciccia F, Cadelo M, Castelli A, Perino A, Licata G. IVIG in APS pregnancy. Lupus 2004;13: 731-735.	Non-systematic review
Tzafettas J, Petropoulos P, Psarra A, Delkos D, Papaloukas C, Giannoulis H, Kalogiros G, Gkoutzioulis F. Early antiplatelet and antithrombotic therapy in patients with a history of recurrent miscarriages of known and unknown aetiology. European journal of obstetrics, gynecology, and reproductive biology 2005;120: 22-26.	Observational cohort study, no control intervention
Visser J, Cohen D, Bloemenkamp KW. Antithrombotic medications and recurrent miscarriage. The New England journal of medicine 2010;363: 887-888; author reply 888.	Author reply
Walker ID, Kujovich JL, Greer IA, Rey E, David M, Salmon JE, Hunt BJ, Zotz RB, Gerhardt A, Scharf RE et al. The use of LMWH in pregnancies at risk: new evidence or perception? Journal of thrombosis and haemostasis : 2005;3: 778-793.	Comment to Brenner 2005
Wechsler B, Huong Du LT, Piette JC. Is there a role for antithrombotic therapy in the prevention of pregnancy loss? Haemostasis 1999;29 Suppl S1: 112-120.	Non-systematic review
Winger EE, Reed JL. Treatment with tumor necrosis factor inhibitors and intravenous immunoglobulin improves live birth rates in women with recurrent spontaneous abortion. American journal of reproductive immunology 2008;60: 8-16.	Not relevant for question
Wisloff F, Crowther M. Evidence-based treatment of the antiphospholipid syndrome: I. Pregnancy failure. Thrombosis research 2004;114: 75-81.	APS treatment
Yang GY, Luo H, Liao X, Liu JP. Chinese herbal medicine for the treatment of recurrent miscarriage: a systematic review of randomized clinical trials. BMC complementary and alternative medicine 2013;13: 320.	Not RPL and thrombophilia
YM AM, Elussein EA, Omer MM, Samaan SI, F AR, Adam I. Heparin and aspirin in pregnant Sudanese women with recurrent miscarriage associated with antiphospholipid antibodies. African journal of reproductive health 2007;11: 95-98.	Study not controlled
Younis JS, Ohel G, Brenner B, Ben-Ami M. Familial thrombophilia--the scientific rationale for thrombophylaxis in recurrent pregnancy loss? Human reproduction 1997;12: 1389-1390.	Debate
Zotz RB, Gerhardt A, Scharf RE. Antithrombotic prophylaxis for women with thrombophilia and pregnancy complications. Journal of thrombosis and haemostasis 2004;2: 1182-1192.	Comment to Brenner 2003

14. WHICH THERAPEUTIC INTERVENTIONS SHOULD BE OFFERED TO PATIENTS WITH RPL DUE TO MALE FACTOR TO INCREASE LIVE BIRTH RATE?

Flowchart



List of excluded papers

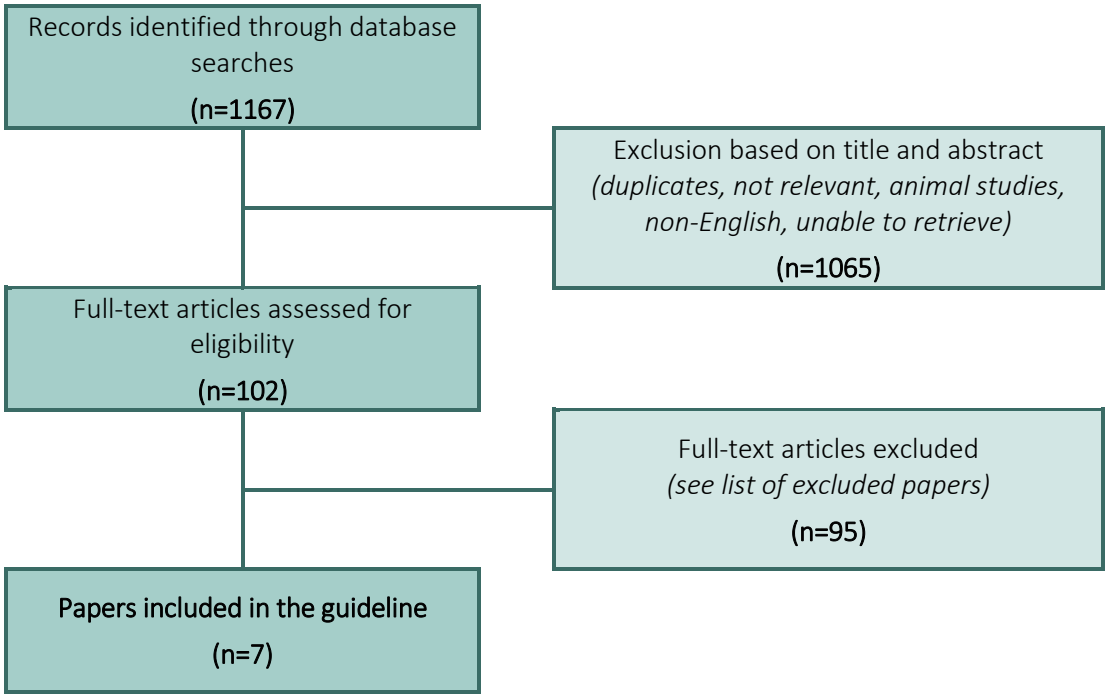
	EXCLUSION CRITERIA
Borges E, Jr., Rossi-Ferragut LM, Pasqualotto FF, dos Santos DR, Rocha CC, Iaconelli A, Jr. Testicular sperm results in elevated miscarriage rates compared to epididymal sperm in azoospermic patients. Sao Paulo medical journal 2002;120: 122-126.	Not RPL: miscarriage rate according to source of sperm
Chen L, Zhou Q, Kinoshita M, Liu L, Zhou D. Recurrent epileptic seizures with multifocal brain MRI lesions after paternal lymphocyte immunization: a causal relationship to multiple sclerosis? Neuropathology 2011;31: 98-99.	Immunotherapy and MS, not RPL
Cowchock FS, Smith JB. Fertility among women with recurrent spontaneous abortions--the effect of paternal cell immunization treatment. American journal of reproductive immunology 1995;33: 176-181.	Immunotherapy in women, not relevant for this question
Evenson DP. Sperm chromatin structure assay (SCSA(R)). Methods in molecular biology 2013;927: 147-164.	Not RPL
Friedler S, Raziel A, Strassburger D, Schachter M, Bern O, Ron-El R. Outcome of ICSI using fresh and cryopreserved-thawed testicular spermatozoa in patients with non-mosaic Klinefelter's syndrome. Human reproduction 2001;16: 2616-2620.	Klinefelter's syndrome, only 2 pregnancies
Friedler S, Raziel A, Strassburger D, Schachter M, Soffer Y, Ron-El R. Factors influencing the outcome of ICSI in patients with obstructive and non-obstructive azoospermia: a comparative study. Human reproduction 2002;17: 3114-3121.	Not RPL: miscarriage rate according to source of sperm
Go KJ, Patel JC, Cunningham DL. The role of assisted reproductive technology in the management of recurrent pregnancy loss. Current opinion in endocrinology, diabetes, and obesity 2009;16: 459-463.	An array of reports on the effects of PGS on embryo implantation

Gupta S, Agarwal A, Banerjee J, Alvarez JG. The role of oxidative stress in spontaneous abortion and recurrent pregnancy loss: a systematic review. Obstetrical & gynecological survey 2007;62: 335-347; quiz 353-334.	General review – no additional data
Hamamah S, Fignon A, Lansac J. The effect of male factors in repeated spontaneous abortion: lesson from in-vitro fertilization and intracytoplasmic sperm injection. Human reproduction update 1997;3: 393-400.	General review- no additional data
He X, Cao Y, Zhang Z, Zhao J, Wei Z, Zhou P, Cong L. Spermatogenesis affects the outcome of ICSI for azoospermic patients rather than sperm retrieval method. Systems biology in reproductive medicine 2010;56: 457-464.	Not RPL: miscarriage rate according to source of sperm
Jeng GT, Scott JR, Burmeister LF. A comparison of meta-analytic results using literature vs individual patient data. Paternal cell immunization for recurrent miscarriage. JAMA 1995;274: 830-836.	Immunotherapy in women, not relevant for this question
Kamal A, Fahmy I, Mansour R, Serour G, Aboulghar M, Ramos L, Kremer J. Does the outcome of ICSI in cases of obstructive azoospermia depend on the origin of the retrieved spermatozoa or the cause of obstruction? A comparative analysis. Fertility and sterility 2010;94: 2135-2140.	Included in chapter on diagnosis
Kano T, Mori T, Furudono M, Ishikawa H, Watanabe H, Kikkawa E, Warita T, Onizuka M, Takahashi M, Maeda Y et al. Human leukocyte antigen may predict outcome of primary recurrent spontaneous abortion treated with paternal lymphocyte alloimmunization therapy. American journal of reproductive immunology 2007;58: 383-387.	Immunotherapy in women, not relevant for this question
Khonina NA, Broitman EV, Shevela EY, Pasman NM, Chernykh ER. Mixed lymphocyte reaction blocking factors (MLR-Bf) as potential biomarker for indication and efficacy of paternal lymphocyte immunization in recurrent spontaneous abortion. Archives of gynecology and obstetrics 2013;288: 933-937.	Immunotherapy in women, not relevant for this question
Mansour Ghanaie M, Asgari SA, Dadrass N, Allahkhah A, Iran-Pour E, Safarinejad MR. Effects of varicocele repair on spontaneous first trimester miscarriage: a randomized clinical trial. Urology journal 2012;9: 505-513.	Varicoele repair – not RPL
Mowbray JF, Gibbings C, Liddell H, Reginald PW, Underwood JL, Beard RW. Controlled trial of treatment of recurrent spontaneous abortion by immunisation with paternal cells. Lancet 1985;1: 941-943.	Immunotherapy in women, not relevant for this question
Naru T, Sulaiman MN, Kidwai A, Ather MH, Waqar S, Virk S, Rizvi JH. Intracytoplasmic sperm injection outcome using ejaculated sperm and retrieved sperm in azoospermic men. Urology journal 2008;5: 106-110.	Not RPL: outcomes after ICSI according to source of sperm
Nicopoullos JD, Gilling-Smith C, Almeida PA, Norman-Taylor J, Grace I, Ramsay JW. Use of surgical sperm retrieval in azoospermic men: a meta-analysis. Fertility and sterility 2004;82: 691-701.	Included in chapter on diagnosis
Oldereid NB, Hanevik HI, Bakkevig I, Romundstad LB, Magnus O, Hazekamp J, Hentemann M, Eikeland SN, Skrede S, Reitan IR et al. Pregnancy outcome according to male diagnosis after ICSI with non-ejaculated sperm compared with ejaculated sperm controls. Reproductive biomedicine online 2014;29: 417-423.	Not RPL: outcomes after ICSI according to source of sperm
Oron G, Fisch B, Sapir O, Wertheimer A, Garor R, Feldberg D, Pinkas H, Ben-Haroush A. Pregnancy outcome after ICSI with thawed testicular sperm from men with non-obstructive azoospermia compared to ICSI with ejaculated sperm from men with severe oligoasthenoteratozoospermia and IVF with normal ejaculated sperm. Gynecological endocrinology 2014;30: 103-106.	Not RPL: outcomes after ICSI according to source of sperm
Pandey MK, Agrawal S. Induction of MLR-Bf and protection of fetal loss: a current double blind randomized trial of paternal lymphocyte immunization for women with recurrent spontaneous abortion. International immunopharmacology 2004;4: 289-298.	Immunotherapy in women, not relevant for this question
Pasqualotto FF, Rossi LM, Guilherme P, Ortiz V, Iaconelli A, Jr., Borges E, Jr. Etiology-specific outcomes of intracytoplasmic sperm injection in azoospermic patients. Fertility and sterility 2005;83: 606-611.	Not RPL: outcomes after ICSI according to source of sperm
Pasqualotto FF, Rossi-Ferragut LM, Rocha CC, Iaconelli A, Jr., Borges E, Jr. Outcome of in vitro fertilization and intracytoplasmic injection of epididymal and testicular sperm obtained from patients with obstructive and nonobstructive azoospermia. The Journal of urology 2002;167: 1753-1756.	Not RPL: miscarriage rate according to source of sperm
Pons I, Cercas R, Villas C, Brana C, Fernandez-Shaw S. One abstinence day decreases sperm DNA fragmentation in 90 % of selected patients. Journal of assisted reproduction and genetics 2013;30: 1211-1218.	Effect of abstinence day on sperm DNA fragmentation (not RPL)

Ramhorst R, Agriello E, Zittermann S, Pando M, Larriba J, Irigoyen M, Cortelezzi M, Auge L, Lombardi E, Etchepareborda JJ et al. Is the paternal mononuclear cells' immunization a successful treatment for recurrent spontaneous abortion? American journal of reproductive immunology 2000;44: 129-135.	Immunotherapy in women, not relevant for this question
Robinson L, Gallos ID, Conner SJ, Rajkhowa M, Miller D, Lewis S, Kirkman-Brown J, Coomarasamy A. The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Human reproduction 2012;27: 2908-2917.	Included in chapter on diagnosis
Ross C, Morriss A, Khairy M, Khalaf Y, Braude P, Coomarasamy A, El-Toukhy T. A systematic review of the effect of oral antioxidants on male infertility. Reproductive biomedicine online 2010;20: 711-723.	Oral antioxidants in infertile men to improve pregnancy rates (not RPL)
Rubio I, Galan A, Larreategui Z, Ayerdi F, Bellver J, Herrero J, Meseguer M. Clinical validation of embryo culture and selection by morphokinetic analysis: a randomized, controlled trial of the EmbryoScope. Fertility and sterility 2014.	Not RPL
Ruixue W, Hongli Z, Zhihong Z, Rulin D, Dongfeng G, Ruizhi L. The impact of semen quality, occupational exposure to environmental factors and lifestyle on recurrent pregnancy loss. Journal of assisted reproduction and genetics 2013;30: 1513-1518.	Included in chapter on diagnosis
Rumbold A, Middleton P, Pan N, Crowther CA. Vitamin supplementation for preventing miscarriage. The Cochrane database of systematic reviews 2011: Cd004073.	Vitamin supplementation for preventing miscarriage (not RPL)
Schwartz D, Mayaux MJ, Guihard-Moscato ML, Czyglik F, David G. Abortion rate in A.I.D. and semen characteristics: a study of 1345 pregnancies. Andrologia 1986;18: 292-298.	Very old and no real data
Twisk M, Mastenbroek S, van Wely M, Heineman MJ, Van der Veen F, Repping S. Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection. The Cochrane database of systematic reviews 2006: Cd005291.	Not RPL
Vissenberg R, Goddijn M. Is there a role for assisted reproductive technology in recurrent miscarriage? Seminars in reproductive medicine 2011;29: 548-556.	General review , no additional data
Wettasinghe TK, Jayasekara RW, Dissanayake VH. Y chromosome microdeletions are not associated with spontaneous recurrent pregnancy loss in a Sinhalese population in Sri Lanka. Human reproduction (Oxford, England) 2010;25: 3152-3156.	Included in chapter on diagnosis
Zhang L, Wang L, Zhang X, Xu G, Zhang W, Wang K, Wang Q, Qiu Y, Li J, Gai L. Sperm chromatin integrity may predict future fertility for unexplained recurrent spontaneous abortion patients. International journal of andrology 2012;35: 752-757.	Diagnosis, not treatment
Zhao J, Zhang Q, Wang Y, Li Y. Whether sperm deoxyribonucleic acid fragmentation has an effect on pregnancy and miscarriage after in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis. Fertility and sterility 2014;102: 998-1005 e1008.	Included in chapter on diagnosis

15. WHICH THERAPEUTIC INTERVENTIONS SHOULD BE OFFERED TO PATIENTS WITH RPL WITH SUSPICION OF IMMUNOLOGICAL BACKGROUND TO INCREASE LIVE BIRTH RATE?

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Alalaf S. Bemiparin versus low dose aspirin for management of recurrent early pregnancy losses due to antiphospholipd antibody syndrome. Archives of gynecology and obstetrics 2012;285: 641-647.	Not relevant for this question
Al-Khateeb GM, Sater MS, Finan RR, Mustafa FE, Al-Busaidi AS, Al-Sulaiti MA, Almawi WY. Analysis of interleukin-18 promoter polymorphisms and changes in interleukin-18 serum levels underscores the involvement of interleukin-18 in recurrent spontaneous miscarriage. Fertility and sterility 2011;96: 921-926.	Not treatment
al-Momen AK, Moghraby SA, el-Rab MO, Gader AM, al-Balla SR, al-Meshari AA, al-Nuaim L. Pregnancy outcome in women with antiphospholipid antibodies. Clinical rheumatology 1993;12: 381-386.	Not relevant for this question
Aoki K, Dudkiewicz AB, Matsuura E, Novotny M, Kaberlein G, Gleicher N. Clinical significance of beta 2-glycoprotein I-dependent anticardiolipin antibodies in the reproductive autoimmune failure syndrome: correlation with conventional antiphospholipid antibody detection systems. American journal of obstetrics and gynecology 1995;172: 926-931.	Implantation failure, not RPL
Bennett SA, Bagot CN, Appiah A, Johns J, Ross J, Roberts LN, Patel RK, Arya R. Women with unexplained recurrent pregnancy loss do not have evidence of an underlying prothrombotic state: experience with calibrated automated thrombography and rotational thromboelastometry. Thrombosis research 2014;133: 892-899.	Not treatment

Bermas BL, Hill JA. Proliferative responses to recall antigens are associated with pregnancy outcome in women with a history of recurrent spontaneous abortion. The Journal of clinical investigation 1997;100: 1330-1334.	Not treatment
Bombell S, McGuire W. Cytokine polymorphisms in women with recurrent pregnancy loss: meta-analysis. The Australian & New Zealand journal of obstetrics & gynaecology 2008;48: 147-154.	Not treatment
Carp HJ. Recurrent miscarriage and hCG supplementation: a review and metaanalysis. Gynecological endocrinology 2010;26: 712-716.	Non-systematic review
Carp HJ, Toder V, Gazit E, Ahiron R, Torchinski A, Mashiach S, Shoenfeld Y. Further experience with intravenous immunoglobulin in women with recurrent miscarriage and a poor prognosis. American journal of reproductive immunology 2001;46: 268-273.	No randomization or blinding
Carp HJ, Toder V, Torchinsky A, Portuguese S, Lipitz S, Gazit E, Mashiach S. Allogenic leukocyte immunization after five or more miscarriages. Recurrent Miscarriage Immunotherapy Trialists Group. Human reproduction 1997;12: 250-255.	Small study
Chernyshov VP, Vodyanik MA, Pisareva SP. Lack of soluble TNF-receptors in women with recurrent spontaneous abortion and possibility for its correction. American journal of reproductive immunology 2005;54: 284-291.	Not treatment
Christiansen OB, Mathiesen O, Husth M, Lauritsen JG, Grunnet N. Placebo-controlled trial of active immunization with third party leukocytes in recurrent miscarriage. Acta obstetricia et gynecologica Scandinavica 1994;73: 261-268.	Included in chapter on treatment unexplained RPL
Christiansen OB, Mathiesen O, Husth M, Rasmussen KL, Ingerslev HJ, Lauritsen JG, Grunnet N. Placebo-controlled trial of treatment of unexplained secondary recurrent spontaneous abortions and recurrent late spontaneous abortions with i.v. immunoglobulin. Human reproduction 1995;10: 2690-2695.	Included in review Egerup 2015- included in chapter on unexplained RPL
Christiansen OB, Pedersen B, Rosgaard A, Husth M. A randomized, double-blind, placebo-controlled trial of intravenous immunoglobulin in the prevention of recurrent miscarriage: evidence for a therapeutic effect in women with secondary recurrent miscarriage. Human reproduction 2002;17: 809-816.	Included in review Egerup 2015- included in chapter on unexplained RPL
Clark P, Walker ID, Langhorne P, Crichton L, Thomson A, Greaves M, Whyte S, Greer IA. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. Blood 2010;115: 4162-4167.	Included in review de Jong 2014
Clifford K, Rai R, Watson H, Franks S, Regan L. Does suppressing luteinising hormone secretion reduce the miscarriage rate? Results of a randomised controlled trial. BMJ (Clinical research ed) 1996;312: 1508-1511.	Included in question 11
Coulam CB, Krysa L, Stern JJ, Bustillo M. Intravenous immunoglobulin for treatment of recurrent pregnancy loss. American journal of reproductive immunology 1995;34: 333-337.	Included in review Egerup 2015- included in chapter on unexplained RPL
Couto E, Barini R, Pinto e Silva JL, de Moraes DR, de Carvalho LM. Anticardiolipin antibody in recurrent spontaneous aborting and fertile women. Sao Paulo medical journal 1998;116: 1760-1765.	Not treatment
Daya S, Gunby J. The effectiveness of allogeneic leukocyte immunization in unexplained primary recurrent spontaneous abortion. Recurrent Miscarriage Immunotherapy Trialists Group. American journal of reproductive immunology 1994;32: 294-302.	recent systematic review available
Daya S, Gunby J, Porter F, Scott J, Clark DA. Critical analysis of intravenous immunoglobulin therapy for recurrent miscarriage. Human reproduction update 1999;5: 475-482.	More recent systematic review available
de Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. The Cochrane database of systematic reviews 2014;7: Cd004734.	Included in chapter on treatment unexplained RPL
Deligiannidis A, Parapanissiou E, Mavroudi A, Papastavrou T. Neonatal thrombocytopenia as side effect of immunotherapy for recurrent spontaneous abortion. American journal of reproductive immunology 2007;57: 167-168.	Case report emphasizing the potential risk of LIT

Dendrinos S, Sakkas E, Makrakis E. Low-molecular-weight heparin versus intravenous immunoglobulin for recurrent abortion associated with antiphospholipid antibody syndrome. International journal of gynaecology and obstetrics 2009;104: 223-225.	Not relevant for this question
Dolitzky M, Inbal A, Segal Y, Weiss A, Brenner B, Carp H. A randomized study of thromboprophylaxis in women with unexplained consecutive recurrent miscarriages. Fertility and sterility 2006;86: 362-366.	Included in meta-analysis de Jong 2014, included in question 16
Elmahashi MO, Elbareg AM, Essadi FM, Ashur BM, Adam I. Low dose aspirin and low-molecular-weight heparin in the treatment of pregnant Libyan women with recurrent miscarriage. BMC research notes 2014;7: 23.	Late start of treatment
Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. The Cochrane database of systematic reviews 2005: Cd002859.	Not relevant for this question
Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. Obstetrics and gynecology 2002;100: 408-413.	Not relevant for this question
Fawzy M, Shokeir T, El-Tatongy M, Warda O, El-Refaiey AA, Mosbah A. Treatment options and pregnancy outcome in women with idiopathic recurrent miscarriage: a randomized placebo-controlled study. Archives of gynecology and obstetrics 2008;278: 33-38.	Included in meta-analysis de Jong 2014, included in question 16
Gatenby PA, Cameron K, Simes RJ, Adelstein S, Bennett MJ, Jansen RP, Shearman RP, Stewart GJ, Whittle M, Doran TJ. Treatment of recurrent spontaneous abortion by immunization with paternal lymphocytes: results of a controlled trial. American journal of reproductive immunology 1993;29: 88-94.	Included in meta-analysis Wong 2014, included in question 16
Gharesi-Fard B, Zolghadri J, Foroughinia L, Tavazoo F, Samsami Dehaghani A. Effectiveness of leukocyte immunotherapy in primary recurrent spontaneous abortion (RSA). Iranian journal of immunology 2007;4: 173-178.	Non randomized comparison of outcome in LIT treated and non-LIT treated RM patients
Giancotti A, La Torre R, Spagnuolo A, D'Ambrosio V, Cerekja A, Piazze J, Chistolini A. Efficacy of three different antithrombotic regimens on pregnancy outcome in pregnant women affected by recurrent pregnancy loss. The journal of maternal-fetal & neonatal medicine 2012;25: 1191-1194.	Included in meta-analysis de Jong 2014, included in question 16
Glueck CJ, Gogenini S, Munjal J, Tracy T, Pranikoff J, Wang P. Factor V Leiden mutation: a treatable etiology for sporadic and recurrent pregnancy loss. Fertility and sterility 2008;89: 410-416.	Not relevant for this question
Goel N, Tuli A, Choudhry R. The role of aspirin versus aspirin and heparin in cases of recurrent abortions with raised anticardiolipin antibodies. Medical science monitor 2006;12: Cr132-136.	Not relevant for this question
Gomaa MF, Elkholy AG, El-Said MM, Abdel-Salam NE. Combined oral prednisolone and heparin versus heparin: the effect on peripheral NK cells and clinical outcome in patients with unexplained recurrent miscarriage. A double-blind placebo randomized controlled trial. Archives of gynecology and obstetrics 2014;290: 757-762.	Included in review Dan 2015, included in question 16
Haas DM, Ramsey PS. Progestogen for preventing miscarriage. The Cochrane database of systematic reviews 2013;10: Cd003511.	Included in chapter on treatment unexplained RPL
Harrison RF. Treatment of habitual abortion with human chorionic gonadotropin: results of open and placebo-controlled studies. European journal of obstetrics, gynecology, and reproductive biology 1985;20: 159-168.	Included in Cochrane review Morley 2013
Hasegawa I, Takakuwa K, Goto S, Yamada K, Sekizuka N, Kanazawa K, Tanaka K. Effectiveness of prednisolone/aspirin therapy for recurrent aborters with antiphospholipid antibody. Human reproduction 1992;7: 203-207.	Not relevant for this question
Hutton B, Sharma R, Fergusson D, Tinmouth A, Hebert P, Jamieson J, Walker M. Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review. BJOG 2007;114: 134-142.	Included in chapter on treatment unexplained RPL
Illeni MT, Marelli G, Parazzini F, Acaia B, Bocciolone L, Bontempelli M, Faden D, Fedele L, Maffeis A, Radici E. Immunotherapy and recurrent abortion: a randomized clinical trial. Human reproduction 1994;9: 1247-1249.	Included in meta-analysis Wong 2014, included in question 16
Jablonowska B, Selbing A, Palfi M, Ernerudh J, Kjellberg S, Lindton B. Prevention of recurrent spontaneous abortion by intravenous	Included in review Egerup 2015- included in chapter on unexplained RPL

immunoglobulin: a double-blind placebo-controlled study. Human reproduction 1999;14: 838-841.	
Kaandorp SP, Goddijn M, van der Post JA, Hutten BA, Verhoeve HR, Hamulyak K, Mol BW, Folkeringa N, Nahuis M, Papatsonis DN et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. The New England journal of medicine 2010;362: 1586-1596.	Included in meta-analysis de Jong 2014, included in question 16
Kalra S, Tuli A, Choudhry R, Raheja S. Prevalence of anticardiolipin antibody IgG in recurrent first trimester abortions and the role of aspirin in its prevention. Medical science monitor : international medical journal of experimental and clinical research 2003;9: Cr213-216.	Not relevant for this question
Karami N, Boroujerdnia MG, Nikbakht R, Khodadadi A. Enhancement of peripheral blood CD56(dim) cell and NK cell cytotoxicity in women with recurrent spontaneous abortion or in vitro fertilization failure. Journal of reproductive immunology 2012;95: 87-92.	Included in chapter on diagnosis
Karhukorpi J, Laitinen T, Kivela H, Tiilikainen A, Hurme M. IL-1 receptor antagonist gene polymorphism in recurrent spontaneous abortion. Journal of reproductive immunology 2003;58: 61-67.	Not relevant for this question
Krause M, Sonntag B, Klamroth R, Heinecke A, Scholz C, Langer C, Scharrer I, Greb RR, von Eckardstein A, Nowak-Gottl U. Lipoprotein (a) and other prothrombotic risk factors in Caucasian women with unexplained recurrent miscarriage. Results of a multicentre case-control study. Thrombosis and haemostasis 2005;93: 867-871.	Not relevant for this question
Kumar A, Begum N, Prasad S, Aggarwal S, Sharma S. Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial. Fertility and sterility 2014.	Included in chapter on treatment unexplained RPL
Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. American journal of obstetrics and gynecology 1996;174: 1584-1589.	Not relevant for this question
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. Fertility and sterility 1999;71: 843-848.	Not relevant for this question
Kutteh WH, Yetman DL, Chantilis SJ, Crain J. Effect of antiphospholipid antibodies in women undergoing in-vitro fertilization: role of heparin and aspirin. Human reproduction (Oxford, England) 1997;12: 1171-1175.	Not relevant for this question
Kwak JY, Kwak FM, Ainbinder SW, Ruiz AM, Beer AE. Elevated peripheral blood natural killer cells are effectively downregulated by immunoglobulin G infusion in women with recurrent spontaneous abortions. American journal of reproductive immunology 1996;35: 363-369.	Not relevant for this question
Laskin CA, Spitzer KA, Clark CA, Crowther MR, Ginsberg JS, Hawker GA, Kingdom JC, Barrett J, Gent M. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. The Journal of rheumatology 2009;36: 279-287.	Not relevant for this question
Lund M, Nielsen HS, Hviid TV, Steffensen R, Nyboe Andersen A, Christiansen OB. Hereditary thrombophilia and recurrent pregnancy loss: a retrospective cohort study of pregnancy outcome and obstetric complications. Human reproduction 2010;25: 2978-2984.	Not relevant for this question
Mak A, Cheung MW, Cheak AA, Ho RC. Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive anti-phospholipid antibodies: a meta-analysis of randomized controlled trials and meta-regression. Rheumatology (Oxford, England) 2010;49: 281-288.	Not relevant for this question
Mantha S, Bauer KA, Zwicker JI. Low molecular weight heparin to achieve live birth following unexplained pregnancy loss: a systematic review. Journal of thrombosis and haemostasis : JTH 2010;8: 263-268.	Not recurrent pregnancy loss
Morley LC, Simpson N, Tang T. Human chorionic gonadotrophin (hCG) for preventing miscarriage. The Cochrane database of systematic reviews 2013;1: Cd008611.	Included in question 11
Mowbray JF, Gibbings C, Liddell H, Reginald PW, Underwood JL, Beard RW. Controlled trial of treatment of recurrent spontaneous abortion by immunisation with paternal cells. Lancet 1985;1: 941-943.	Included in chapter on treatment unexplained RPL

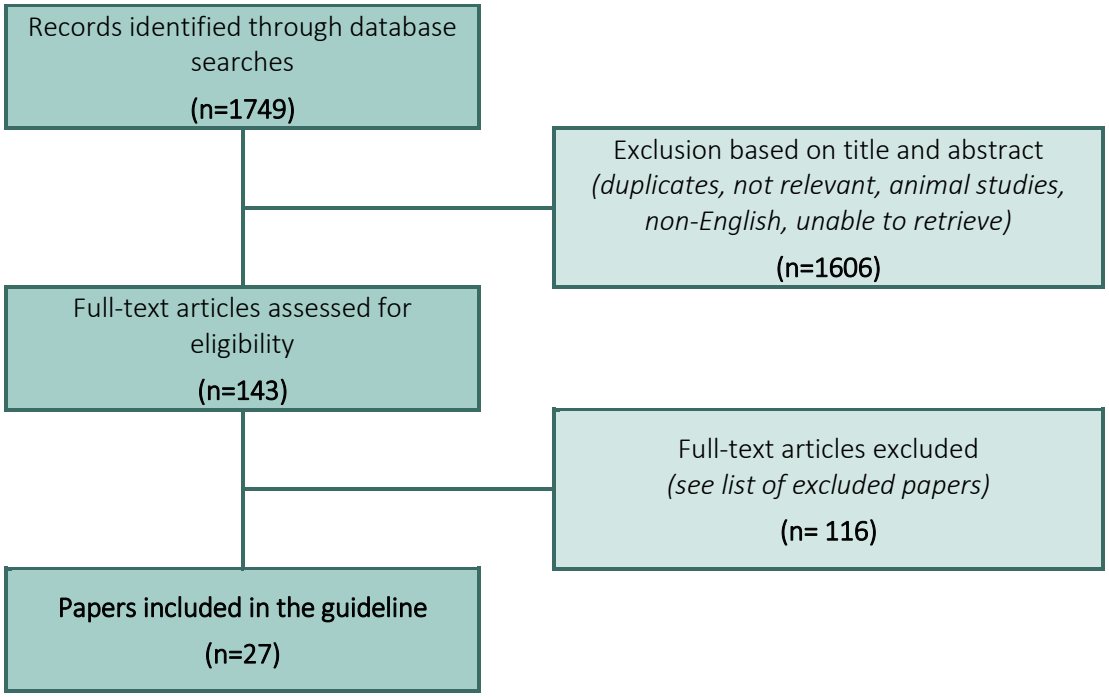
Mueller-Eckhardt G, Mallmann P, Neppert J, Lattermann A, Melk A, Heine O, Pfeiffer R, Zingsem J, Domke N, Mohr-Pennert A. Immunogenetic and serological investigations in nonpregnant and in pregnant women with a history of recurrent spontaneous abortions. German RSA/IVIG Study Group. Journal of reproductive immunology 1994;27: 95-109.	Included in chapter on diagnosis
Neppert J, Mueller-Eckhardt G, Neumeyer H, Malchus R, Kiefel V, Gerhard I, Kuhn U, Westphal E, Harpprecht J. Pregnancy-maintaining antibodies: workshop report (Giessen, 1988). Journal of reproductive immunology 1989;15: 159-167.	workshop report
Nielsen HS, Wu F, Aghai Z, Steffensen R, van Halteren AG, Spierings E, Christiansen OB, Miklos D, Goulmy E. H-Y antibody titers are increased in unexplained secondary recurrent miscarriage patients and associated with low male : female ratio in subsequent live births. Human reproduction 2010;25: 2745-2752.	Included in chapter on diagnosis
Ober C, Karrison T, Odem RR, Barnes RB, Branch DW, Stephenson MD, Baron B, Walker MA, Scott JR, Schreiber JR. Mononuclear-cell immunisation in prevention of recurrent miscarriages: a randomised trial. Lancet 1999;354: 365-369.	Included in meta-analysis Wong 2014, included in question 16
Ogasawara MS, Aoki K, Katano K, Ozaki Y, Suzumori K. Factor XII but not protein C, protein S, antithrombin III, or factor XIII is a predictor of recurrent miscarriage. Fertility and sterility 2001;75: 916-919.	Not treatment
Opatrny L, David M, Kahn SR, Shrier I, Rey E. Association between antiphospholipid antibodies and recurrent fetal loss in women without autoimmune disease: a metaanalysis. The Journal of rheumatology 2006;33: 2214-2221.	Not treatment
Pandey MK, Agrawal S. Induction of MLR-Bf and protection of fetal loss: a current double blind randomized trial of paternal lymphocyte immunization for women with recurrent spontaneous abortion. International immunopharmacology 2004;4: 289-298.	Included in meta-analysis Wong 2014, included in question 16
Pandey MK, Thakur S, Agrawal S. Lymphocyte immunotherapy and its probable mechanism in the maintenance of pregnancy in women with recurrent spontaneous abortion. Archives of gynecology and obstetrics 2004;269: 161-172.	Not relevant for this question
Pattison NS, Chamley LW, Birdsall M, Zanderigo AM, Liddell HS, McDougall J. Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. American journal of obstetrics and gynecology 2000;183: 1008-1012.	Not relevant for this question
Perino A, Vassiliadis A, Vucetich A, Colacurci N, Menato G, Cignitti M, Semprini AE. Short-term therapy for recurrent abortion using intravenous immunoglobulins: results of a double-blind placebo-controlled Italian study. Human reproduction 1997;12: 2388-2392.	Included in review Egerup 2015- included in chapter on unexplained RPL
Perricone R, De Carolis C, Giacomelli R, Guarino MD, De Sanctis G, Fontana L. GM-CSF and pregnancy: evidence of significantly reduced blood concentrations in unexplained recurrent abortion efficiently reverted by intravenous immunoglobulin treatment. American journal of reproductive immunology 2003;50: 232-237.	Irrelevant outcome measure. Changes in GM-CSF in plasma after IvIg to RM patients, No untreated controls
Perricone R, De Carolis C, Kroegler B, Greco E, Giacomelli R, Cipriani P, Fontana L, Perricone C. Intravenous immunoglobulin therapy in pregnant patients affected with systemic lupus erythematosus and recurrent spontaneous abortion. Rheumatology (Oxford, England) 2008;47: 646-651.	Not relevant for this question - SLE
Petri M, Golbus M, Anderson R, Whiting-O'Keefe Q, Corash L, Hellmann D. Antinuclear antibody, lupus anticoagulant, and anticardiolipin antibody in women with idiopathic habitual abortion. A controlled, prospective study of forty-four women. Arthritis Rheum 1987;30: 601-606.	Not relevant for this question
Quenby S, Kalumbi C, Bates M, Farquharson R, Vince G. Prednisolone reduces preconceptual endometrial natural killer cells in women with recurrent miscarriage. Fertility and sterility 2005;84: 980-984.	Included in chapter on diagnosis
Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ 1997;314: 253-257.	Not relevant for this question

Ramhorst R, Agriello E, Zittermann S, Pando M, Larriba J, Irigoyen M, Cortelezzi M, Auge L, Lombardi E, Etchepareborda JJ et al. Is the paternal mononuclear cells' immunization a successful treatment for recurrent spontaneous abortion? American journal of reproductive immunology 2000;44: 129-135.	Not relevant for this question
Russell P, Anderson L, Lieberman D, Tremellen K, Yilmaz H, Cheerala B, Sacks G. The distribution of immune cells and macrophages in the endometrium of women with recurrent reproductive failure I: Techniques. Journal of reproductive immunology 2011;91: 90-102.	not treatment
Russu M, Stanculescu R, Nastasia S, Paun M, Mubarak N, Marin JA, Lachanas I. Pregnancy outcomes following preconception, early and late administration of vaginal micronized progesterone for recurrent pregnancy loss Ginecoro. 2009, pp. 10-15.	Not relevant for this question
Scarpellini F, Sbracia M. Use of granulocyte colony-stimulating factor for the treatment of unexplained recurrent miscarriage: a randomised controlled trial. Human reproduction 2009;24: 2703-2708.	Included in chapter on treatment unexplained RPL
Steck T, Giess R, Suetterlin MW, Bolland M, Wiest S, Poehls UG, Dietl J. Leukaemia inhibitory factor (LIF) gene mutations in women with unexplained infertility and recurrent failure of implantation after IVF and embryo transfer. European journal of obstetrics, gynecology, and reproductive biology 2004;112: 69-73.	Not relevant for this question
Steffensen R, Christiansen OB, Bennett EP, Jersild C. HLA-E polymorphism in patients with recurrent spontaneous abortion. Tissue antigens 1998;52: 569-572.	Not relevant for this question
Stephenson MD, Dreher K, Houlihan E, Wu V. Prevention of unexplained recurrent spontaneous abortion using intravenous immunoglobulin: a prospective, randomized, double-blinded, placebo-controlled trial. American journal of reproductive immunology (New York, NY : 1989) 1998;39: 82-88.	Included in review Egerup 2015- included in chapter on unexplained RPL
Stephenson MD, Kutteh WH, Purkiss S, Librach C, Schultz P, Houlihan E, Liao C. Intravenous immunoglobulin and idiopathic secondary recurrent miscarriage: a multicentered randomized placebo-controlled trial. Human reproduction (Oxford, England) 2010;25: 2203-2209.	Included in review Egerup 2015- included in chapter on unexplained RPL
Stern C, Chamley L, Hale L, Kloss M, Speirs A, Baker HW. Antibodies to beta2 glycoprotein I are associated with in vitro fertilization implantation failure as well as recurrent miscarriage: results of a prevalence study. Fertility and sterility 1998;70: 938-944.	Non-systematic review
Stern JJ, Coulam CB. Current status of immunologic recurrent pregnancy loss. Current opinion in obstetrics & gynecology 1993;5: 252-259.	Non-systematic review
Su MT, Lin SH, Chen YC. Association of sex hormone receptor gene polymorphisms with recurrent pregnancy loss: a systematic review and meta-analysis. Fertility and sterility 2011;96: 1435-1444.e1431.	Not relevant for this question
Sugiura-Ogasawara M, Ozaki Y, Sonta S, Makino T, Suzumori K. Exposure to bisphenol A is associated with recurrent miscarriage. Human reproduction 2005;20: 2325-2329.	Not relevant for this question
Tebo AE, Jaskowski TD, Hill HR, Branch DW. Clinical relevance of multiple antibody specificity testing in anti-phospholipid syndrome and recurrent pregnancy loss. Clinical and experimental immunology 2008;154: 332-338.	Not relevant for this question
Triolo G, Ferrante A, Ciccia F, Accardo-Palumbo A, Perino A, Castelli A, Giarratano A, Licata G. Randomized study of subcutaneous low molecular weight heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. Arthritis Rheum 2003;48: 728-731.	Included in review Egerup 2015- included in chapter on unexplained RPL
Tulppala M, Marttunen M, Soderstrom-Anttila V, Foudila T, Ailus K, Palosuo T, Ylikorkala O. Low-dose aspirin in prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production. Human reproduction 1997;12: 1567-1572.	Included in review de Jong 2014; included in question 16
Umapathy S, Shankarkumar A, Ramrakhiyani V, Ghosh K. Role of anti-human lymphocyte culture cytotoxic antibodies in recurrent spontaneous pregnancy loss women. Journal of human reproductive sciences 2011;4: 17-19.	Not relevant for this question

Unander AM, Norberg R, Arfors L, Enskog A, Haeger M, Lindholm A, Robbins D, Siosteen C, Soderstrom T, Stigendal L et al. Opinions on treatment of women with habitual abortion based on investigations for blocking antibody and autoantibodies. American journal of reproductive immunology (New York, NY : 1989) 1991;26: 32-37.	Non-systematic review
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. Human reproduction update 2011;17: 605-619.	Not relevant for this question
Vaquero E, Lazzarin N, De Carolis C, Valensise H, Moretti C, Ramanini C. Mild thyroid abnormalities and recurrent spontaneous abortion: diagnostic and therapeutical approach. American journal of reproductive immunology 2000;43: 204-208.	Discussed in question 11
Visser J, Ulander VM, Helmerhorst FM, Lampinen K, Morin-Papunen L, Bloemenkamp KW, Kaaja RJ. Thromboprophylaxis for recurrent miscarriage in women with or without thrombophilia. HABENOX: a randomised multicentre trial. Thrombosis and haemostasis 2011;105: 295-301.	Not relevant for this question
Wong L, Porter T, Jesus G. Recurrent early pregnancy loss and antiphospholipid antibodies: where do we stand? Lupus 2014;23: 1226-1228.	Non-systematic review
Wong LF, Porter TF, Scott JR. Immunotherapy for recurrent miscarriage. The Cochrane database of systematic reviews 2014;10: Cd000112.	Included in chapter on treatment unexplained RPL
Zhang B, Liu T, Wang Z. Association of tumor necrosis factor-alpha gene promoter polymorphisms (-308G/A, -238G/A) with recurrent spontaneous abortion: a meta-analysis. Human immunology 2012;73: 574-579.	Included in chapter on diagnosis
Ziakas PD, Pavlou M, Voulgarelis M. Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. Obstetrics and gynecology 2010;115: 1256-1262.	Not relevant for this question

16. WHICH THERAPEUTIC INTERVENTIONS SHOULD BE OFFERED TO PATIENTS WITH UNEXPLAINED RPL TO INCREASE LIVE BIRTH RATE?

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Agrawal S, Kishore R, Halder A, Sharma A, Sharma RK, Das V, Shukla BR, Agarwal SS. Outcome of pregnancy in women with recurrent spontaneous abortion following immunotherapy with allogeneic lymphocytes. Human reproduction 1995;10: 2280-2284.	Non-randomised study of outcome in LIT treated RM patients who produced or did not produce blocking antibodies after LIT
Agrawal S, Pandey MK, Pandey A. Prevalence of MLR blocking antibodies before and after immunotherapy. Journal of hematotherapy & stem cell research 2000;9: 257-262.	Irrelevant outcome measure: level. of block abs
Amin AF, Shaaban OM, Bediawy MA. N-acetyl cysteine for treatment of recurrent unexplained pregnancy loss. Reproductive biomedicine online 2008;17: 722-726.	No randomization or blinding in the two cohorts
Ata B, Tan SL, Shehata F, Holzer H, Buckett W. A systematic review of intravenous immunoglobulin for treatment of unexplained recurrent miscarriage. Fertility and sterility 2011;95: 1080-1085.e1081-1082.	Questions on the criteria for inclusion and exclusion of RCTs
Badawy AM, Khiary M, Sherif LS, Hassan M, Ragab A, Abdelall I. Low-molecular weight heparin in patients with recurrent early miscarriages of unknown aetiology. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 2008;28: 280-284.	Included in meta-analysis de Jong 2014
Balasch J, Creus M, Fabregues F, Civico S, Carmona F, Martorell J, Vanrell JA. In-vitro fertilization treatment for unexplained recurrent abortion: a pilot study. Human reproduction 1996;11: 1579-1582.	Very small study, inadequate control group
Bernardi LA, Cohen RN, Stephenson MD. Impact of subclinical hypothyroidism in women with recurrent early pregnancy loss. Fertility and sterility 2013;100: 1326-1331.	Thyroxine treatment, discussed in question 11

Betts D, Smith CA, Hannah DG. Acupuncture as a therapeutic treatment option for threatened miscarriage. BMC complementary and alternative medicine 2012;12: 20.	Non-systematic review
Carp HJ, Ahiron R, Mashiach S, Schonfeld Y, Gazit E, Toder V. Intravenous immunoglobulin in women with five or more abortions. American journal of reproductive immunology (New York, NY : 1989) 1996;35: 360-362.	Pilot study of IvIg to 10 patients with 5 or more miscarriages. No controls
Carp HJ, Ben-Shlomo I, Toder V, Nebel L, Mashiach S. Congenital malformations after immunotherapy for habitual abortion: is there an increase? Gynecologic and obstetric investigation 1993;36: 198-201.	Study of fetal malformations in 180 pts after LIT and 85 pts who chose not to get LIT
Carp HJ, Toder V, Gazit E, Ahiron R, Torchinski A, Mashiach S, Shoenfeld Y. Further experience with intravenous immunoglobulin in women with recurrent miscarriage and a poor prognosis. American journal of reproductive immunology 2001;46: 268-273.	No randomization or blinding
Carp HJ. Recurrent miscarriage and hCG supplementation: a review and metaanalysis. Gynecological endocrinology 2010;26: 712-716.	Non-systematic review
Christiansen OB, Mathiesen O, Husth M, Rasmussen KL, Ingerslev HJ, Lauritsen JG, Grunnet N. Placebo-controlled trial of treatment of unexplained secondary recurrent spontaneous abortions and recurrent late spontaneous abortions with i.v. immunoglobulin. Human reproduction 1995;10: 2690-2695.	Included in review Egerup 2015
Christiansen OB, Mathiesen O, Lauritsen JG, Grunnet N. Intravenous immunoglobulin treatment of women with multiple miscarriages. Human reproduction 1992;7: 718-722.	Small cohort of IvIg treated RM patients
Christiansen OB, Pedersen B, Rosgaard A, Husth M. A randomized, double-blind, placebo-controlled trial of intravenous immunoglobulin in the prevention of recurrent miscarriage: evidence for a therapeutic effect in women with secondary recurrent miscarriage. Human reproduction 2002;17: 809-816.	Included in review Egerup 2015
Clark DA, Coulam CB, Daya S, Chaouat G. Unexplained sporadic and recurrent miscarrage in the new millennium: a critical analysis of immune mechanisms and treatments. Human reproduction update 2001;7: 501-511.	non-systematic review
Clark DA. Cell-surface CD200 may predict efficacy of paternal mononuclear leukocyte immunotherapy in treatment of human recurrent pregnancy loss. American journal of reproductive immunology 2009;61: 75-84.	Comparison of LBR in RM patients in relation to number of CD200+ cells injected by LIT. No control group
Clark P, Walker ID, Langhorne P, Crichton L, Thomson A, Greaves M, Whyte S, Greer IA. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. Blood 2010;115: 4162-4167.	Included in meta-analysis de Jong 2014
Coomarasamy A, Truchanowicz EG, Rai R. Does first trimester progesterone prophylaxis increase the live birth rate in women with unexplained recurrent miscarriages? BMJ 2011;342: d1914.	Most included studies old and low quality
Coulam CB, Acacio B. Does immunotherapy for treatment of reproductive failure enhance live births? American journal of reproductive immunology 2012;67: 296-304.	Non-systematic review
Coulam CB, Krysa L, Stern JJ, Bustillo M. Intravenous immunoglobulin for treatment of recurrent pregnancy loss. American journal of reproductive immunology 1995;34: 333-337.	Included in review Egerup 2015
Coulam CB, Stephenson M, Stern JJ, Clark DA. Immunotherapy for recurrent pregnancy loss: analysis of results from clinical trials. American journal of reproductive immunology 1996;35: 352-359.	Review referring to older SRs on LIT and an older RCT on IvIg
Coulam CB, Stern JJ, Bustillo M. Ultrasonographic findings of pregnancy losses after treatment for recurrent pregnancy loss: intravenous immunoglobulin versus placebo. Fertility and sterility 1994;61: 248-251.	Not a RCT and outcome is not relevant to search outcome (Blighted ovum or IUFD)
Cowchock FS, Smith JB. Fertility among women with recurrent spontaneous abortions--the effect of paternal cell immunization treatment. Am J Reprod Immunol 1995;33: 176-181.	Comparing LIT before conception with LIT after conception. Irrelevant outcome
Creus M, Calafell JM, Civico S, Fabregues F, Carmona F, Vanrell JA, Balasch J. Materno-fetal immunogenetic disparity: the biological basis for in vitro fertilization treatment in patients with unexplained recurrent abortion? American journal of reproductive immunology 2003;50: 420-426.	Invalid comparison
Dan S, Wei W, Yichao S, Hongbo C, Shenmin Y, Jiaxiong W, Hong L. Effect of Prednisolone Administration on Patients with Unexplained Recurrent	Inappropriate inclusion of data Tang 2009-2013

Miscarriage and in Routine Intracytoplasmic Sperm Injection: A Meta-Analysis. Am J Reprod Immunol 2015;74: 89-97.	
Daya S, Gunby J, Clark DA. Intravenous immunoglobulin therapy for recurrent spontaneous abortion: a meta-analysis. American journal of reproductive immunology 1998;39: 69-76.	More recent systematic review available
Daya S, Gunby J, Porter F, Scott J, Clark DA. Critical analysis of intravenous immunoglobulin therapy for recurrent miscarriage. Human reproduction update 1999;5: 475-482.	More recent systematic review available
Daya S, Gunby J. The effectiveness of allogeneic leukocyte immunization in unexplained primary recurrent spontaneous abortion. Recurrent Miscarriage Immunotherapy Trialists Group. American journal of reproductive immunology 1994;32: 294-302.	recent systematic review available
Deligiannidis A, Parapanissiou E, Mavroudi A, Papastavrou T. Neonatal thrombocytopenia as side effect of immunotherapy for recurrent spontaneous abortion. American journal of reproductive immunology 2007;57: 167-168.	Case report emphasizing the potential risk of LIT
Di Nisio M, Peters L, Middeldorp S. Anticoagulants for the treatment of recurrent pregnancy loss in women without antiphospholipid syndrome. The Cochrane database of systematic reviews 2005: Cd004734.	Outdated Cochrane review
Di Renzo GC, Giardina I, Clerici G, Mattei A, Alajmi AH, Gerli S. The role of progesterone in maternal and fetal medicine. Gynecological endocrinology 2012;28: 925-932.	Non-systematic review
Dolitzky M, Inbal A, Segal Y, Weiss A, Brenner B, Carp H. A randomized study of thromboprophylaxis in women with unexplained consecutive recurrent miscarriages. Fertility and sterility 2006;86: 362-366.	Included in meta-analysis de Jong 2014
Duckitt K, Qureshi A. Recurrent miscarriage. Clinical evidence 2011;2011.	Review not up-to-date, last reseach in Jan 2010
El-Far M, El-Motwally Ael G, Hashem IA, Bakry N. Biochemical role of intravaginal sildenafil citrate as a novel antiabortive agent in unexplained recurrent spontaneous miscarriage: first clinical study of four case reports from Egypt. Clinical chemistry and laboratory medicine : CCLM / FESCC 2009;47: 1433-1438.	4 cases treated with sildenafil
Elmahashi MO, Elbareg AM, Essadi FM, Ashur BM, Adam I. Low dose aspirin and low-molecular-weight heparin in the treatment of pregnant Libyan women with recurrent miscarriage. BMC research notes 2014;7: 23.	Late start of treatment
El-Zibdeh MY. Dydrogesterone in the reduction of recurrent spontaneous abortion. The Journal of steroid biochemistry and molecular biology 2005;97: 431-434.	Included in meta-analysis Haas 2013
Fawzy M, Shokeir T, El-Tatongy M, Warda O, El-Refaiey AA, Mosbah A. Treatment options and pregnancy outcome in women with idiopathic recurrent miscarriage: a randomized placebo-controlled study. Archives of gynecology and obstetrics 2008;278: 33-38.	Included in meta-analysis de Jong 2014
Gatenby PA, Cameron K, Simes RJ, Adelstein S, Bennett MJ, Jansen RP, Shearman RP, Stewart GJ, Whittle M, Doran TJ. Treatment of recurrent spontaneous abortion by immunization with paternal lymphocytes: results of a controlled trial. American journal of reproductive immunology 1993;29: 88-94.	Included in meta-analysis Wong 2014
Gharesi-Fard B, Zolghadri J, Foroughinia L, Tavazoo F, Samsami Dehaghani A. Effectiveness of leukocyte immunotherapy in primary recurrent spontaneous abortion (RSA). Iranian journal of immunology :2007;4: 173-178.	Non randomized comparison of outcome in LIT treated and non-LIT treated RM patients
Ghosh S, Chattopadhyay R, Goswami S, Chaudhury K, Chakravarty B, Ganesh A. Assessment of sub-endometrial blood flow parameters following dydrogesterone and micronized vaginal progesterone administration in women with idiopathic recurrent miscarriage: a pilot study. The journal of obstetrics and gynaecology research 2014;40: 1871-1876.	Comparisons of two different ways of administration is not relevant. No info about treatment start
Giancotti A, La Torre R, Spagnuolo A, D'Ambrosio V, Cerekja A, Piazze J, Chistolini A. Efficacy of three different antithrombotic regimens on pregnancy outcome in pregnant women affected by recurrent pregnancy loss. The journal of maternal-fetal & neonatal medicine 2012;25: 1191-1194.	Included in meta-analysis de Jong 2014

Gilman-Sachs A, Harris D, Beer A, Beaman KD. Inhibition of binding of anti-CD3 antibodies to paternal lymphocytes correlates with failure of immunotherapy for treatment of recurrent spontaneous abortions. Journal of reproductive immunology 1990;17: 41-51.	Study of the predictive value of two color flow cytometry cross match abs. after LIT in 34 RM patients
Go KJ, Patel JC, Cunningham DL. The role of assisted reproductive technology in the management of recurrent pregnancy loss. Current opinion in endocrinology, diabetes, and obesity 2009;16: 459-463.	non-systematic review
Gris JC, Neveu S, Tailland ML, Courtieu C, Mares P, Schved JF. Use of a low-molecular weight heparin (enoxaparin) or of a phenformin-like substance (moroxydine chloride) in primary early recurrent aborters with an impaired fibrinolytic capacity. Thrombosis and haemostasis 1995;73: 362-367.	Patients selected due to presence of fibrinolytic disturbances
Gris JC. LMWH have no place in recurrent pregnancy loss: debate-against the motion. Thrombosis research 2011;127 Suppl 3: S110-112.	Debate, no new results
Harrison RF. Human chorionic gonadotrophin (hCG) in the management of recurrent abortion; results of a multi-centre placebo-controlled study. European journal of obstetrics, gynecology, and reproductive biology 1992;47: 175-179.	Included in Cochrane review Morley 2013
Harrison RF. Treatment of habitual abortion with human chorionic gonadotropin: results of open and placebo-controlled studies. European journal of obstetrics, gynecology, and reproductive biology 1985;20: 159-168.	Included in Cochrane review Morley 2013
Heine O, Mueller-Eckhardt G. Intravenous immune globulin in recurrent abortion. Clinical and experimental immunology 1994;97 Suppl 1: 39-42.	Non-systematic review
Hirahara F, Andoh N, Sawai K, Hirabuki T, Uemura T, Minaguchi H. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials. Fertility and sterility 1998;70: 246-252.	Included in question 11 (hyperprolactinemia)
Hussain M, El-Hakim S, Cahill DJ. Progesterone supplementation in women with otherwise unexplained recurrent miscarriages. Journal of human reproductive sciences 2012;5: 248-251.	The two groups are too different to allow valid comparisons
Illeni MT, Marelli G, Parazzini F, Acaia B, Bocciolone L, Bontempelli M, Faden D, Fedele L, Maffeis A, Radici E. Immunotherapy and recurrent abortion: a randomized clinical trial. Human reproduction (Oxford, England) 1994;9: 1247-1249.	Included in meta-analysis Wong 2014
Jablonowska B, Palfi M, Matthiesen L, Selbing A, Kjellberg S, Ernerudh J. T and B lymphocyte subsets in patients with unexplained recurrent spontaneous abortion: IVIG versus placebo treatment. American journal of reproductive immunology 2002;48: 312-318.	Irrelevant outcome measure: changes in T and B lymphocytes
Jablonowska B, Selbing A, Palfi M, Ernerudh J, Kjellberg S, Lindton B. Prevention of recurrent spontaneous abortion by intravenous immunoglobulin: a double-blind placebo-controlled study. Human reproduction 1999;14: 838-841.	Included in review Egerup 2015
Jong PG, Kaandorp SP, Nisio M, Goddijn M, Middeldorp S. Aspirin or anticoagulants not effective for treating recurrent miscarriage in women without antiphospholipid syndrome: An updated systematic review. Human reproduction. 2013, pp. i143-i144.	Conference abstract
Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. The Cochrane database of systematic reviews 2009: Cd004734.	Outdated Cochrane review
Kaandorp SP, Goddijn M, van der Post JA, Hutten BA, Verhoeve HR, Hamulyak K, Mol BW, Folkeringa N, Nahuis M, Papatsonis DN et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. The New England journal of medicine 2010;362: 1586-1596.	Included in meta-analysis de Jong 2014
Katano K, Ogasawara M, Aoyama T, Ozaki Y, Kajiura S, Aoki K. Clinical trial of immunostimulation with a biological response modifier in unexplained recurrent spontaneous abortion patients. Journal of clinical immunology 1997;17: 472-477.	Comparison of 23 RM injected with killed streptococcal preparation due to high NK activity, compared with 205 patients who got LIT. No random allocation
Kheshtchin N, Gharagozloo M, Andalib A, Ghahiri A, Maracy MR, Rezaei A. The expression of Th1- and Th2-related chemokine receptors in women with recurrent miscarriage: the impact of lymphocyte immunotherapy. American journal of reproductive immunology (New York, NY : 1989) 2010;64: 104-112.	Irrelevant outcome measure: change of T-cell receptors after LIT, nothing about pregnancy outcome

Khonina NA, Broitman EV, Shevela EY, Pasman NM, Chernykh ER. Mixed lymphocyte reaction blocking factors (MLR-Bf) as potential biomarker for indication and efficacy of paternal lymphocyte immunization in recurrent spontaneous abortion. Archives of gynecology and obstetrics 2013;288: 933-937.	Only comparison of LBR in RM patients with and without blocking antibody. No testing of LIT
Kwak JY, Kwak FM, Ainbinder SW, Ruiz AM, Beer AE. Elevated peripheral blood natural killer cells are effectively downregulated by immunoglobulin G infusion in women with recurrent spontaneous abortions. American journal of reproductive immunology 1996;35: 363-369.	Irrelevant outcome measure: CD56+ NK cells in RM pts. before and after IvIg
Lash GE, Bulmer JN, Innes BA, Drury JA, Robson SC, Quenby S. Prednisolone treatment reduces endometrial spiral artery development in women with recurrent miscarriage. Angiogenesis 2011;14: 523-532.	Irrelevant outcome measure: measurements of change in vascular smooth muscle cells from the endometrium
Lazzarin N, Vaquero E, Exacoustos C, Bertonotti E, Romanini ME, Arduini D. Low-dose aspirin and omega-3 fatty acids improve uterine artery blood flow velocity in women with recurrent miscarriage due to impaired uterine perfusion. Fertility and sterility 2009;92: 296-300.	Irrelevant Outcome: Uterine perfusion. Not pregnancy outcome.
Li L, Dou L, Leung Ping C, Chung Tony Kwok H, Wang Chi C. Chinese herbal medicines for unexplained recurrent miscarriage Cochrane Database of Systematic Reviews. 2013. John Wiley & Sons, Ltd.	Protocol for SR of Chinese herbal medicine, no results
Li L, Dou LX, Neilson JP, Leung PC, Wang CC. Adverse outcomes of Chinese medicines used for threatened miscarriage: a systematic review and meta-analysis. Human reproduction update 2012;18: 504-524.	Irrelevant patient group (threatened miscarriage)
Malinowski A, Prochowska A, Banasik M, Wilczynski J, Szpakowski M, Zeman K, Oszukowski P, Lerch E. Clinical and immunological condition of newborns of mothers treated for recurrent spontaneous abortions with paternal lymphocytes immunization. European journal of obstetrics, gynecology, and reproductive biology 1997;73: 55-61.	no data usable for evaluating treatment effect
Mantha S, Bauer KA, Zwicker JI. Low molecular weight heparin to achieve live birth following unexplained pregnancy loss: a systematic review. Journal of thrombosis and haemostasis : JTH 2010;8: 263-268.	Not recurrent pregnancy loss
Maruyama T, Makino T, Iwasaki K, Sugi T, Saito S, Umeuchi M, Ozawa N, Matsubayashi H, Nozawa S. The influence of intravenous immunoglobulin treatment on maternal immunity in women with unexplained recurrent miscarriage. American journal of reproductive immunology (New York, NY : 1989) 1994;31: 7-18.	Case series of 8 patients
Miyashita Y, Waguri M, Nakanishi I, Suehara N, Fujita T. Successful pregnancy with low molecular weight heparin in two women with recurrent miscarriage of unknown etiology. American journal of reproductive immunology (New York, NY : 1989) 2003;49: 90-92.	2 cases only
Monien S, Kadecki O, Baumgarten S, Salama A, Dorner T, Kiesewetter H. Use of heparin in women with early and late miscarriages with and without thrombophilia. Clinical and applied thrombosis 2009;15: 636-644.	No control group or randomisation
Morikawa M, Yamada H, Kato EH, Shimada S, Kishi T, Yamada T, Kobashi G, Fujimoto S. Massive intravenous immunoglobulin treatment in women with four or more recurrent spontaneous abortions of unexplained etiology: down-regulation of NK cell activity and subsets. American journal of reproductive immunology 2001;46: 399-404.	Case series of 14 patients, no controls
Morikawa M, Yamada H, Kato EH, Shimada S, Sakuragi N, Fujimoto S, Minakami H. Live birth rate varies with gestational history and etiology in women experiencing recurrent spontaneous abortion. European journal of obstetrics, gynecology, and reproductive biology 2003;109: 21-26.	Massive IvIg treatment compared with LDA or luteal support in a non-randomsied trial in RM
Morley LC, Simpson N, Tang T. Human chorionic gonadotrophin (hCG) for preventing miscarriage. The Cochrane database of systematic reviews 2013;1: Cd008611.	Included in question 11
Mueller-Eckhardt G. Immunotherapy with intravenous immunoglobulin for prevention of recurrent pregnancy loss: European experience. American journal of reproductive immunology 1994;32: 281-285.	Combined review of one RCT and some pilot studies of IvIg
Munne S, Chen S, Fischer J, Colls P, Zheng X, Stevens J, Escudero T, Oter M, Schoolcraft B, Simpson JL et al. Preimplantation genetic diagnosis reduces pregnancy loss in women aged 35 years and older with a history of recurrent miscarriages. Fertility and sterility 2005;84: 331-335.	Invalid comparison

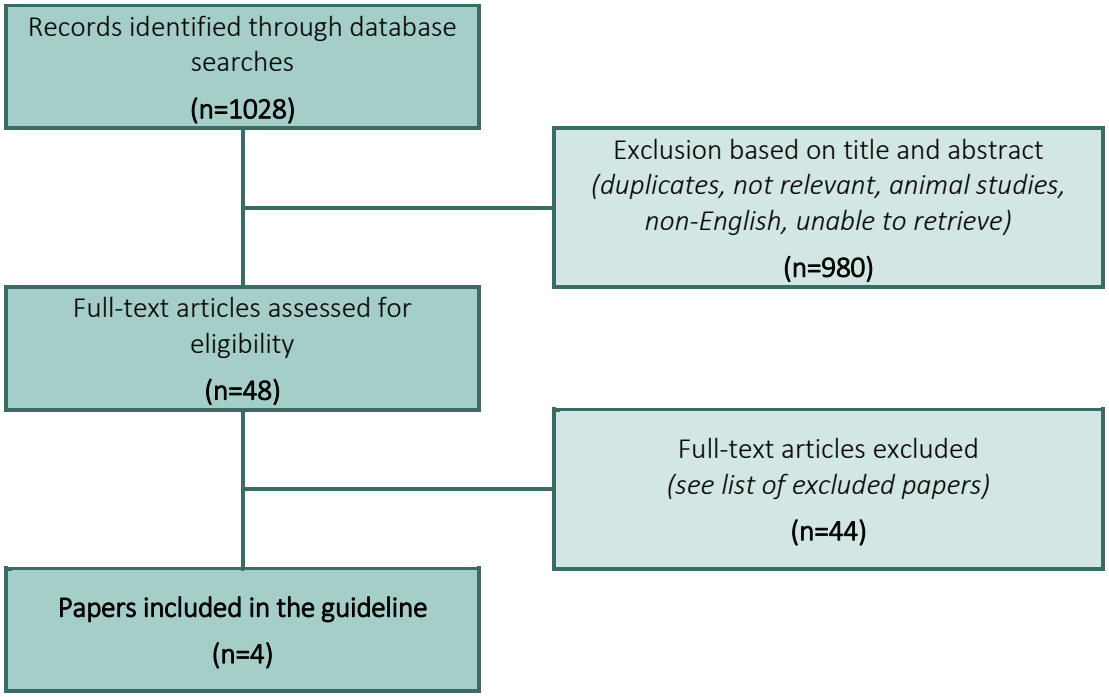
Nonaka T, Takakuwa K, Ooki I, Akashi M, Yokoo T, Kikuchi A, Tanaka K. Results of immunotherapy for patients with unexplained primary recurrent abortions--prospective non-randomized cohort study. American journal of reproductive immunology (New York, NY : 1989) 2007;58: 530-536.	Comparison of LBR in RM pts without block abs. who got LIT, untreated pts with block abs. and pts who did not want LIT
Ober C, Karrison T, Odem RR, Barnes RB, Branch DW, Stephenson MD, Baron B, Walker MA, Scott JR, Schreiber JR. Mononuclear-cell immunisation in prevention of recurrent miscarriages: a randomised trial. Lancet 1999;354: 365-369.	Included in meta-analysis Wong 2014
Pang LH, Li MJ, Li M, Xu H, Wei ZL. Not every subseptate uterus requires surgical correction to reduce poor reproductive outcome. International journal of gynaecology and obstetrics 2011;115: 260-263.	Not relevant for this question
Perino A, Vassiliadis A, Vucetich A, Colacurci N, Menato G, Cignitti M, Semprini AE. Short-term therapy for recurrent abortion using intravenous immunoglobulins: results of a double-blind placebo-controlled Italian study. Human reproduction 1997;12: 2388-2392.	Included in review Egerup 2015
Perricone R, De Carolis C, Giacomelli R, Guarino MD, De Sanctis G, Fontana L. GM-CSF and pregnancy: evidence of significantly reduced blood concentrations in unexplained recurrent abortion efficiently reverted by intravenous immunoglobulin treatment. American journal of reproductive immunology (New York, NY : 1989) 2003;50: 232-237.	Irrelevant outcome measure. Changes in GM-CSF in plasma after IvIg to RM patients, No untreated controls
Price M, Kelsberg G, Safranek S, Damitz B. Clinical inquiries. What treatments prevent miscarriage after recurrent pregnancy loss? The Journal of family practice 2005;54: 892, 894.	Non-systematic review
Quenby S, Farquharson RG. Human chorionic gonadotropin supplementation in recurring pregnancy loss: a controlled trial. Fertility and sterility 1994;62: 708-710.	Included in Cochrane review Morley 2013
Raziel A, Herman A, Bukovsky I, Caspi E, Ron-el R. Intravenous immunoglobulin treatment of pregnant patients with unexplained recurrent abortions. Human reproduction 1996;11: 711-715.	Small review of case-series
Raziel A, Herman A, Strassburger D, Soffer Y, Bukovsky I, Ron-El R. The outcome of in vitro fertilization in unexplained habitual aborters concurrent with secondary infertility. Fertility and sterility 1997;67: 88-92.	No new information
Remohi J, Gallardo E, Levy M, Valbuena D, de los Santos MJ, Simon C, Pellicer A. Oocyte donation in women with recurrent pregnancy loss. Human reproduction 1996;11: 2048-2051.	oocyte donation for unexplained RM
Reznikoff-Etievant MF, Cayol V, Zou GM, Abuaf N, Robert A, Johanet C, Milliez J. Habitual abortions in 678 healthy patients: investigation and prevention. Human reproduction 1999;14: 2106-2109.	Quality unacceptable
Rigal D, Vermot-Desroches C, Heitz S, Bernaud J, Alfonsi F, Monier JC. Effects of intravenous immunoglobulins (IVIG) on peripheral blood B, NK, and T cell subpopulations in women with recurrent spontaneous abortions: specific effects on LFA-1 and CD56 molecules. Clinical immunology and immunopathology 1994;71: 309-314.	Case series of 13 RM patients treated with IvIg
Robinson CJ. Aspirin alone or combined with nadroparin did not increase live birth rates in women with unexplained recurrent miscarriage: Commentary Annals of internal medicine. 2010, pp. Jc47.	Summary of the study by Kaandorp et al NEJM 2010
Salman SA, Shaaban OM, Zahran KM, Fathalla MM, Anan MA. Low molecular weight heparin (LMWH) for treatment of recurrent miscarriage negatively tested for anti phospholipid antibodies: A randomized controlled trial Fertility and sterility. 2012, pp. S191.	Conference abstract
Scott JR, Pattison N. Human chorionic gonadotrophin for recurrent miscarriage. The Cochrane database of systematic reviews 2000: Cd000101.	Outdated Cochrane review
Siklosi GS, Banhidy FG, Acs N. Fundamental role of folliculo-luteal function in recurrent miscarriage. Archives of gynecology and obstetrics 2012;286: 1299-1305.	Unclear how patients and pregnancies with insuff progesterone in the placebo group were handled
Stephenson MD, Dreher K, Houlihan E, Wu V. Prevention of unexplained recurrent spontaneous abortion using intravenous immunoglobulin: a prospective, randomized, double-blinded, placebo-controlled trial. American journal of reproductive immunology 1998;39: 82-88.	Included in review Egerup 2015
Stephenson MD, Kutteh WH, Purkiss S, Librach C, Schultz P, Houlihan E, Liao C. Intravenous immunoglobulin and idiopathic secondary recurrent	Included in review Egerup 2015

miscarriage: a multicentered randomized placebo-controlled trial. Human reproduction 2010;25: 2203-2209.	
Sugiura-Ogasawara M, Ozaki Y, Nakanishi T, Sato T, Suzumori N, Kumagai K. Occasional antiphospholipid antibody positive patients with recurrent pregnancy loss also merit aspirin therapy: a retrospective cohort-control study. American journal of reproductive immunology 2008;59: 235-241.	Study of RM patients with pos APL in a single test. No randomisation
Szekeres-Bartho J, Balasch J. Progestagen therapy for recurrent miscarriage. Human reproduction update 2008;14: 27-35.	Non-systematic review
Szekeres-Bartho J. Progesterone-mediated immunomodulation in pregnancy: its relevance to leukocyte immunotherapy of recurrent miscarriage. Immunotherapy 2009;1: 873-882.	Non-systematic review
Tanaka T, Umesaki N, Nishio J, Maeda K, Kawamura T, Araki N, Ogita S. Neonatal thrombocytopenia induced by maternal anti-HLA antibodies: a potential side effect of allogenic leukocyte immunization for unexplained recurrent aborters. Journal of reproductive immunology 2000;46: 51-57.	Case report stressing the risk of neonatal thrombocytopenia after LIT
Tang AW, Alfirevic Z, Turner MA, Drury J, Quenby S. Prednisolone Trial: Study protocol for a randomised controlled trial of prednisolone for women with idiopathic recurrent miscarriage and raised levels of uterine natural killer (uNK) cells in the endometrium. Trials 2009;10: 102.	Study protocol
Tempfer CB, Kurz C, Bentz EK, Unfried G, Walch K, Czizek U, Huber JC. A combination treatment of prednisone, aspirin, folate, and progesterone in women with idiopathic recurrent miscarriage: a matched-pair study. Fertility and sterility 2006;86: 145-148.	The folate only group declined combined treatment. A matched subset of these was selected as controls. No information about how and when matching was done
Toth B, Jeschke U, Rogenhofer N, Scholz C, Wurfel W, Thaler CJ, Makrigiannakis A. Recurrent miscarriage: current concepts in diagnosis and treatment. Journal of reproductive immunology 2010;85: 25-32.	Irrelevant outcome measure: Study about glycoprotein binding in placentas from early pregnancy loss
Tulppala M, Marttunen M, Soderstrom-Anttila V, Ailus K, Palosuo T, Ylikorkala O. Low dose aspirin in the prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production Human reproduction 1997, pp. 191.	Conference abstract
Tulppala M, Marttunen M, Soderstrom-Anttila V, Foudila T, Ailus K, Palosuo T, Ylikorkala O. Low-dose aspirin in prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production. Human reproduction 1997;12: 1567-1572.	Included in meta-analysis de Jong 2014
Tzafettas J, Petropoulos P, Psarra A, Delkos D, Papaloukas C, Giannoulis H, Kalogiros G, Gkoutzioulis F. Early antiplatelet and antithrombotic therapy in patients with a history of recurrent miscarriages of known and unknown aetiology. European journal of obstetrics, gynecology, and reproductive biology 2005;120: 22-26.	No controls or randomisation
Unander AM, Norberg R, Arfors L, Enskog A, Haeger M, Lindholm A, Robbins D, Siosteen C, Soderstrom T, Stigendal L et al. Opinions on treatment of women with habitual abortion based on investigations for blocking antibody and autoantibodies. American journal of reproductive immunology 1991;26: 32-37.	Non-systematic review
van den Heuvel MJ, Peralta CG, Hatta K, Han VK, Clark DA. Decline in number of elevated blood CD3(+) CD56(+) NKT cells in response to intravenous immunoglobulin treatment correlates with successful pregnancy. American journal of reproductive immunology 2007;58: 447-459.	Observational study: of LBR in relation to different NK cell subsets after IvIg
van Iddekinge B, Hofmeyr GJ, Bezwoda WR, Wadee AA, Van Rooy P. Recurrent spontaneous abortion: histocompatibility between partners, response to immune therapy, and subsequent reproductive performance. American journal of reproductive immunology 1993;30: 37-44.	Case-series of 16 RM patients, reviews available
Vaquero E, Lazzarin N, De Carolis C, Valensise H, Moretti C, Ramanini C. Mild thyroid abnormalities and recurrent spontaneous abortion: diagnostic and therapeutical approach. American journal of reproductive immunology 2000;43: 204-208.	Thyroxine treatment, discussed in question 11
Vissenberg R, Goddijn M. Is there a role for assisted reproductive technology in recurrent miscarriage? Seminars in reproductive medicine 2011;29: 548-556.	non-systematic review

Visser J, Ulander VM, Helmerhorst FM, Lampinen K, Morin-Papunen L, Bloemenkamp KW, Kaaja RJ. Thromboprophylaxis for recurrent miscarriage in women with or without thrombophilia. HABENOX: a randomised multicentre trial. Thrombosis and haemostasis 2011;105: 295-301.	Included in meta-analysis de Jong 2014
Walch K, Hefler L, Nagele F. Oral dydrogesterone treatment during the first trimester of pregnancy: the prevention of miscarriage study (PROMIS). A double-blind, prospectively randomized, placebo-controlled, parallel group trial. The journal of maternal-fetal & neonatal medicine 2005;18: 265-269.	Protocol for RCT, no results
Walch KT, Huber JC. Progesterone for recurrent miscarriage: truth and deceptions. Best practice & research Clinical obstetrics & gynaecology 2008;22: 375-389.	Non-systematic review
Yamada H, Kishida T, Kobayashi N, Kato EH, Hoshi N, Fujimoto S. Massive immunoglobulin treatment in women with four or more recurrent spontaneous primary abortions of unexplained aetiology. Human reproduction 1998;13: 2620-2623.	Case report 11 pts treated with IvIg
Yamada H, Morikawa M, Furuta I, Kato EH, Shimada S, Iwabuchi K, Minakami H. Intravenous immunoglobulin treatment in women with recurrent abortions: increased cytokine levels and reduced Th1/Th2 lymphocyte ratio in peripheral blood. American journal of reproductive immunology 2003;49: 84-89.	Irrelevant outcome measure: changes in Th cytokines after IvIg in 9 RM patients
Yokoo T, Takakuwa K, Ooki I, Kikuchi A, Tamura M, Tanaka K. Alteration of TH1 and TH2 cells by intracellular cytokine detection in patients with unexplained recurrent abortion before and after immunotherapy with the husband's mononuclear cells. Fertility and sterility 2006;85: 1452-1458.	Irrelevant outcome: changes in Th cell subsets after LIT
Yovich JL, Turner SR, Draper R. Medroxyprogesterone acetate therapy in early pregnancy has no apparent fetal effects. Teratology 1988;38: 135-144.	Irrelevant outcome: fetal malformations in progesterone vs non-progesterone treated cohorts.
Zolghadri J, Momtahan M, Alborzi S, Mohammadinejad A, Khosravi D. Pregnancy outcome in patients with early recurrent abortion following laparoscopic tubal corneal interruption of a fallopian tube with hydrosalpinx. Fertility and sterility 2006;86: 149-151.	Very small study – hydrosalpinx discussed in question 12

17. WHICH THERAPEUTIC INTERVENTIONS COULD BE OFFERED TO ALL PATIENTS, IRRESPECTIVE OF A CAUSE, TO INCREASE LIVE BIRTH RATE?

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Arck PC, Hecher K, Solano ME. B Cells in Pregnancy: Functional Promiscuity or Tailored Function? Biology of reproduction 2014.	theory only
Bailey S, Bailey C, Boivin J, Cheong Y, Reading I, Macklon N. A feasibility study for a randomised controlled trial of the Positive Reappraisal Coping Intervention, a novel supportive technique for recurrent miscarriage. BMJ Open 2015;5: e007322.	proposed feasibility study
Basille C, Frydman R, El Aly A, Hesters L, Fanchin R, Tachdjian G, Steffann J, LeLorc'h M, Achour-Frydman N. Preimplantation genetic diagnosis: state of the art. European journal of obstetrics, gynecology, and reproductive biology 2009;145: 9-13.	Non-systematic review
Betts D, Smith CA, Hannah DG. Acupuncture as a therapeutic treatment option for threatened miscarriage. BMC complementary and alternative medicine 2012;12: 20.	threatened miscarriage
Carp HJ, Dirnfeld M, Dor J, Grudzinskas JG. ART in recurrent miscarriage: preimplantation genetic diagnosis/screening or surrogacy? Human reproduction 2004;19: 1502-1505.	Included in review Franssen 2011, included in question 10
Carrington B, Sacks G, Regan L. Recurrent miscarriage: pathophysiology and outcome. Current opinion in obstetrics & gynecology 2005;17: 591-597.	Published before systematic review Franssen 2011 and Musters 2011 (included in question 10)
Christiansen OB, Nielsen HS, Kolte AM. Future directions of failed implantation and recurrent miscarriage research. Reproductive biomedicine online 2006;13: 71-83.	Non-systematic review – not enough evidence

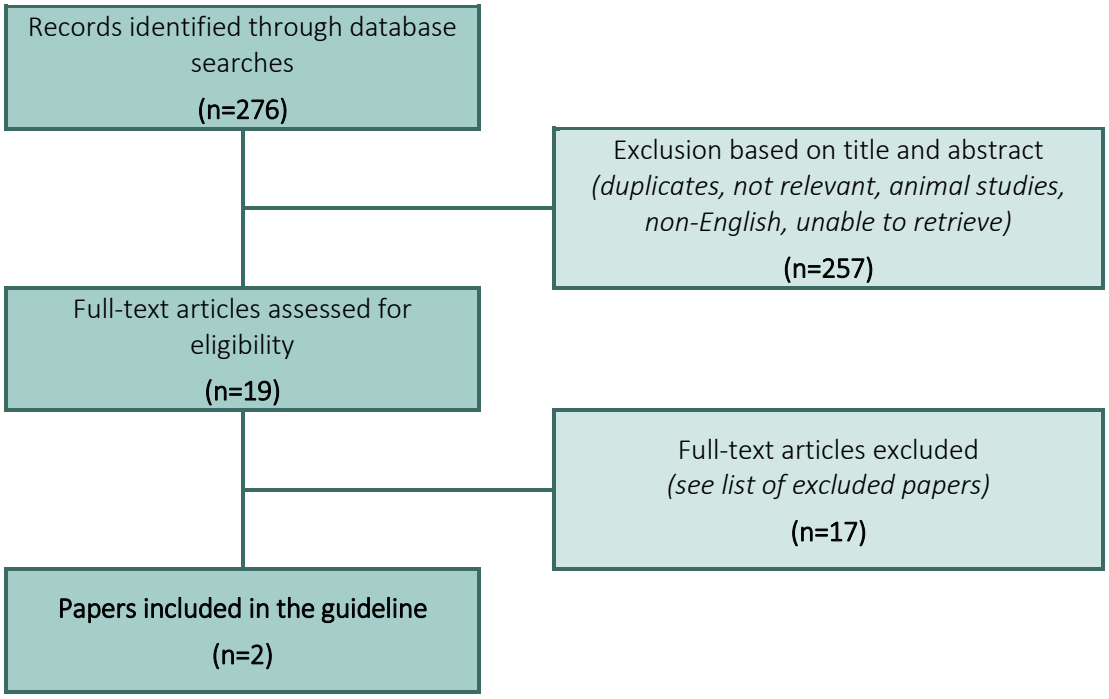
Christiansen OB, Nybo Andersen AM, Bosch E, Daya S, Delves PJ, Hviid TV, Kutteh WH, Laird SM, Li TC, van der Ven K. Evidence-based investigations and treatments of recurrent pregnancy loss. Fertility and sterility 2005;83: 821-839.	Non-systematic review
Doroski DM. How Humanae vitae has advanced reproductive health. The Linacre quarterly 2014;81: 286-294.	infertility only miscarriage rates not reported
Engels H, Eggermann T, Caliebe A, Jelska A, Schubert R, Schuler HM, Panasiuk B, Zaremba J, Latos-Bielenska A, Jakubowski L et al. Genetic counseling in Robertsonian translocations der(13;14): frequencies of reproductive outcomes and infertility in 101 pedigrees. American journal of medical genetics Part A 2008;146a: 2611-2616.	Infertility – not RPL
Fauser BC. Preimplantation genetic screening: the end of an affair? Human reproduction (Oxford, England) 2008;23: 2622-2625.	editorial
Franssen MT, Musters AM, van der Veen F, Repping S, Leschot NJ, Bossuyt PM, Goddijn M, Korevaar JC. Reproductive outcome after PGD in couples with recurrent miscarriage carrying a structural chromosome abnormality: a systematic review. Human reproduction update 2011;17: 467-475.	RPL with chromosomal abnormality - included in question 10
Go KJ, Patel JC, Cunningham DL. The role of assisted reproductive technology in the management of recurrent pregnancy loss. Current opinion in endocrinology, diabetes, and obesity 2009;16: 459-463.	Non-systematic review
Hatasaka HH, Varner MW. Recurrent pregnancy loss. Current opinion in obstetrics & gynecology 1994;6: 503-509.	Non-systematic review
Jauniaux E, Farquharson RG, Christiansen OB, Exalto N. Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. Human reproduction (Oxford, England) 2006;21: 2216-2222.	Guideline
Keymolen K, Staessen C, Verpoest W, Michiels A, Bonduelle M, Haentjens P, Vanderelst J, Liebaers I. A proposal for reproductive counselling in carriers of Robertsonian translocations: 10 years of experience with preimplantation genetic diagnosis. Human reproduction (Oxford, England) 2009;24: 2365-2371.	Carriers of Robertsonian translocations
Li L, Dou LX, Neilson JP, Leung PC, Wang CC. Adverse outcomes of Chinese medicines used for threatened miscarriage: a systematic review and meta-analysis. Human reproduction update 2012;18: 504-524.	Cochrane review of 2016 (same authors) included
Li L, Leung PC, Chung TK, Wang CC. Systematic Review of Chinese Medicine for Miscarriage during Early Pregnancy. Evidence-based complementary and alternative medicine : eCAM 2014;2014: 753856.	Cochrane review of 2016 (same authors) included
Li L, Tang LY, Man GC, Yeung BH, Lau CB, Leung PC, Wang CC. Potential reproductive toxicity of Largehead Atractylodes Rhizome, the most commonly used Chinese medicine for threatened miscarriage. Human reproduction 2011;26: 3280-3288.	threatened miscarriage
Li TC. Recurrent miscarriage: principles of management. Human reproduction 1998;13: 478-482.	Expert opinion
Munne S, Chen S, Fischer J, Colls P, Zheng X, Stevens J, Escudero T, Oter M, Schoolcraft B, Simpson JL et al. Preimplantation genetic diagnosis reduces pregnancy loss in women aged 35 years and older with a history of recurrent miscarriages. Fertility and sterility 2005;84: 331-335.	Included in review Musters 2011, included in question 10
Musters AM, Repping S, Korevaar JC, Mastenbroek S, Limpens J, van der Veen F, Goddijn M. Pregnancy outcome after preimplantation genetic screening or natural conception in couples with unexplained recurrent miscarriage: a systematic review of the best available evidence. Fertility and sterility 2011;95: 2153-2157.	Included in question 10
Nardo LG, Sallam HN. Progesterone supplementation to prevent recurrent miscarriage and to reduce implantation failure in assisted reproduction cycles. Reproductive biomedicine online 2006;13: 47-57.	Published before systematic review Franssen 2011 and Musters 2011 (included in question 10)
Ota K, Dambaeva S, Han AR, Beaman K, Gilman-Sachs A, Kwak-Kim J. Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity. Human reproduction 2014;29: 208-219.	Included in question 11
Pellicer A, Rubio C, Vidal F, Minguez Y, Gimenez C, Egozcue J, Remohi J, Simon C. In vitro fertilization plus preimplantation genetic diagnosis in patients with recurrent miscarriage: an analysis of chromosome	Small study, not relevant for this question

abnormalities in human preimplantation embryos. Fertility and sterility 1999;71: 1033-1039.	
Ray JG, Laskin CA. Folic acid and homocyst(e)ine metabolic defects and the risk of placental abruption, pre-eclampsia and spontaneous pregnancy loss: A systematic review. Placenta 1999;20: 519-529.	Not RPL
Remohi J, Gallardo E, Levy M, Valbuena D, de los Santos MJ, Simon C, Pellicer A. Oocyte donation in women with recurrent pregnancy loss. Human reproduction (Oxford, England) 1996;11: 2048-2051.	Small study (8 patients) with high FSH
Rubio C, Buendia P, Rodrigo L, Mercader A, Mateu E, Peinado V, Delgado A, Milan M, Mir P, Simon C et al. Prognostic factors for preimplantation genetic screening in repeated pregnancy loss. Reproductive biomedicine online 2009;18: 687-693.	Not treatment
Rubio C, Rodrigo L, Perez-Cano I, Mercader A, Mateu E, Buendia P, Remohi J, Simon C, Pellicer A. FISH screening of aneuploidies in preimplantation embryos to improve IVF outcome. Reproductive biomedicine online 2005;11: 497-506.	Published before systematic review Franssen 2011 and Musters 2011 (included in question 10)
Ruixue W, Hongli Z, Zhihong Z, Rulin D, Dongfeng G, Ruizhi L. The impact of semen quality, occupational exposure to environmental factors and lifestyle on recurrent pregnancy loss Journal of assisted reproduction and genetics. 2013, pp. 1513-1518.	Included in question 7 (not treatment)
Santjohanser C, Knieper C, Franz C, Hirv K, Meri O, Schleyer M, Wurfel W, Toth B. Granulocyte-colony stimulating factor as treatment option in patients with recurrent miscarriage. Archivum immunologiae et therapiae experimentalis 2013;61: 159-164.	Included in question 16
Shields LE, Serafini PC, Schenken RS, Moore CM. Chromosomal analysis of pregnancy losses in patients undergoing assisted reproduction. Journal of assisted reproduction and genetics 1992;9: 57-60.	Published before systematic review Franssen 2011 and Musters 2011 (included in question 10)
Stephenson M, Kutteh W. Evaluation and management of recurrent early pregnancy loss. Clinical obstetrics and gynecology 2007;50: 132-145.	Non-systematic review
Sugiura-Ogasawara M, Ozaki Y, Suzumori N. Management of recurrent miscarriage. The journal of obstetrics and gynaecology research 2014;40: 1174-1179.	expert opinion psychological support needed
Swanson A, Strawn E, Lau E, Bick D. Preimplantation genetic diagnosis: technology and clinical applications. WMJ : official publication of the State Medical Society of Wisconsin 2007;106: 145-151.	
Tham E, Schliep K, Stanford J. Natural procreative technology for infertility and recurrent miscarriage: outcomes in a Canadian family practice. Canadian family physician Medecin de famille canadien 2012;58: e267-274.	infertility only miscarriage rates not reported
Toth B, Jeschke U, Rogenhofer N, Scholz C, Wurfel W, Thaler CJ, Makrigiannakis A. Recurrent miscarriage: current concepts in diagnosis and treatment. Journal of reproductive immunology 2010;85: 25-32.	theory only
Tzafettas J, Petropoulos P, Psarra A, Delkos D, Papaloukas C, Giannoulis H, Kalogiros G, Gkoutzioulis F. Early antiplatelet and antithrombotic therapy in patients with a history of recurrent miscarriages of known and unknown aetiology. European journal of obstetrics, gynecology, and reproductive biology 2005;120: 22-26.	Not relevant for this question
Tzioras S, Polyzos NP, Economides DL. How do you solve the problem of recurrent miscarriage? Reproductive biomedicine online 2009;19: 296-297.	Non-systematic review
Van den Berg MM, Vissenberg R, Goddijn M. Recurrent miscarriage clinics. Obstetrics and gynecology clinics of North America 2014;41: 145-155.	Included for organization of care
van den Boogaard E, Goddijn M, Leschot NJ, Veen F, Kremer JA, Hermens RP. Development of guideline-based quality indicators for recurrent miscarriage. Reproductive biomedicine online 2010;20: 267-273.	Not relevant for question
Vidal F, Gimenez C, Rubio C, Simon C, Pellicer A, Santalo J, Egozcue J. FISH preimplantation diagnosis of chromosome aneuploidy in recurrent pregnancy wastage. Journal of assisted reproduction and genetics 1998;15: 310-313.	3 cases

Werlin LB, Rodi I, Decherney A, Marello E, Hill D, Munne S. Preimplantation genetic diagnosis (PGD) as a beneficial tool in women with recurrent pregnancy loss (RPL) and advanced maternal age (AMA) Fertility and sterility. 2004, pp. S241.	Small study
Winger EE, Reed JL. Treatment with tumor necrosis factor inhibitors and intravenous immunoglobulin improves live birth rates in women with recurrent spontaneous abortion. American journal of reproductive immunology 2008;60: 8-16.	Included in question 15

18. How should care for the RPL patient be organised?

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Alijotas-Reig J, Garrido-Gimenez C. Current concepts and new trends in the diagnosis and management of recurrent miscarriage. Obstetrical & gynecological survey 2013;68: 445-466.	Non-systematic review
Cameron MJ, Penney GC. Terminology in early pregnancy loss: what women hear and what clinicians write. The journal of family planning and reproductive health care 2005;31: 313-314.	Usage of patient focused terminology in case notes.
Christiansen OB, Steffensen R, Nielsen HS, Varming K. Multifactorial etiology of recurrent miscarriage and its scientific and clinical implications. Gynecologic and obstetric investigation 2008;66: 257-267.	no input on RM clinic organisation
Habayeb OM, Konje JC. The one-stop recurrent miscarriage clinic: an evaluation of its effectiveness and outcome. Human reproduction 2004;19: 2952-2958.	Not relevant for this question
Ievine CH, Cumming G. Memorial services offered following an early pregnancy loss in Scotland. The practising midwife 2015;18: 23-26.	Early pregnancy loss, not RPL
Khan RA, Drudy L, Sheehan J, Harrison RF, Geary M. Early pregnancy loss: how do men feel? Irish medical journal 2004;97: 217-218.	Early pregnancy loss, not RPL
Kolte AM, Bernardi LA, Christiansen OB, Quenby S, Farquharson RG, Goddijn M, Stephenson MD. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE special interest group, early pregnancy. Human reproduction 2014.	Terminology for pregnancy loss
Kolte AM, Olsen LR, Mikkelsen EM, Christiansen OB, Nielsen HS. Depression and emotional stress is highly prevalent among women with recurrent pregnancy loss. Human reproduction 2015;30: 777-782.	Included in section on psychological impact of RPL

Li TC. Recurrent miscarriage: principles of management. Human reproduction (Oxford, England) 1998;13: 478-482.	Non-systematic review
Matthiesen L, Kalkunte S, Sharma S. Multiple pregnancy failures: an immunological paradigm. American journal of reproductive immunology 2012;67: 334-340.	Not relevant for this question
Nawroth F, Foth D. One-stop recurrent miscarriage clinic and hysteroscopy--an urgent combination? Human reproduction 2005;20: 2976-2979.	Letter to the editor : comments to Habayeb OM, Konje JC.(2005)
Nikcevic AV, Tunkel SA, Nicolaides KH. Psychological outcomes following missed abortions and provision of follow-up care. Ultrasound in obstetrics & gynecology 1998;11: 123-128.	Not RPL
Nothnagle M, Prine L, Goodman S. Benefits of comprehensive reproductive health education in family medicine residency. Family medicine 2008;40: 204-207.	Reproductive health education
Nynas J, Narang P, Kolikonda MK, Lippmann S. Depression and Anxiety Following Early Pregnancy Loss: Recommendations for Primary Care Providers. The primary care companion for CNS disorders 2015;17.	Early pregnancy loss, not RPL
Prine LW, MacNaughton H. Office management of early pregnancy loss. American family physician 2011;84: 75-82.	early pregnancy loss, not RPL
Tham E, Schliep K, Stanford J. Natural procreative technology for infertility and recurrent miscarriage: outcomes in a Canadian family practice. Canadian family physician Medecin de famille canadien 2012;58: e267-274.	RPL patients not assessed seperately
Whitman-Elia GF, Baxley EG. A primary care approach to the infertile couple. The Journal of the American Board of Family Practice / American Board of Family Practice 2001;14: 33-45.	Infertility, not RPL