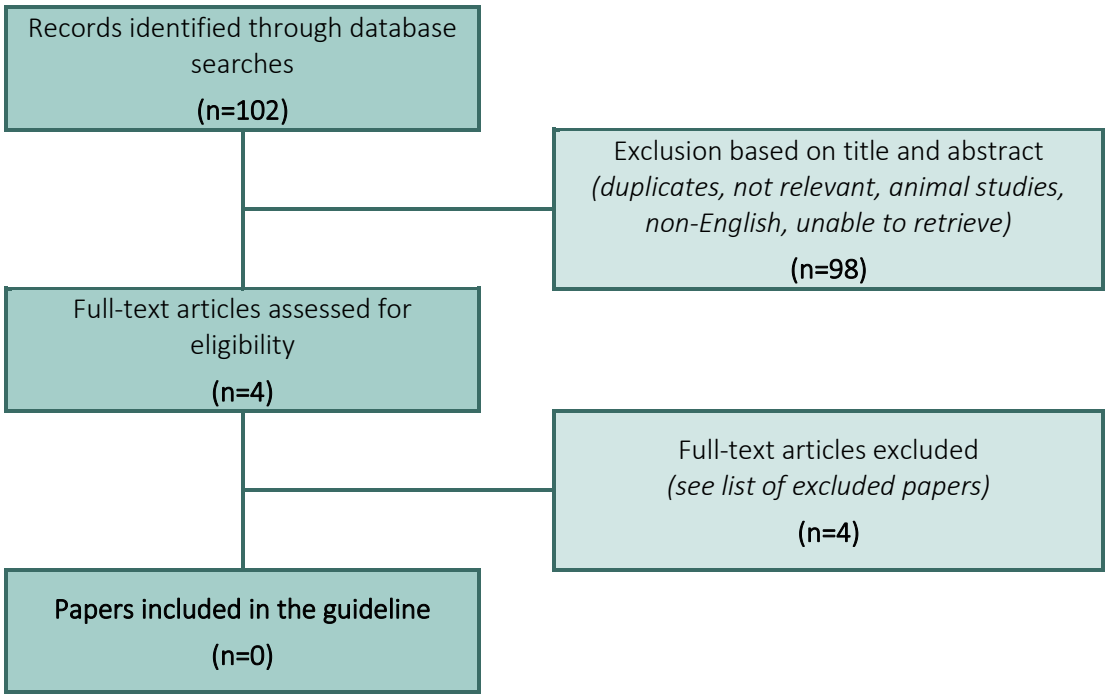
Annex 9: Literature study report: Flowcharts and list of excluded studies

1. How should care for the RM patient be organised?

Flowchart

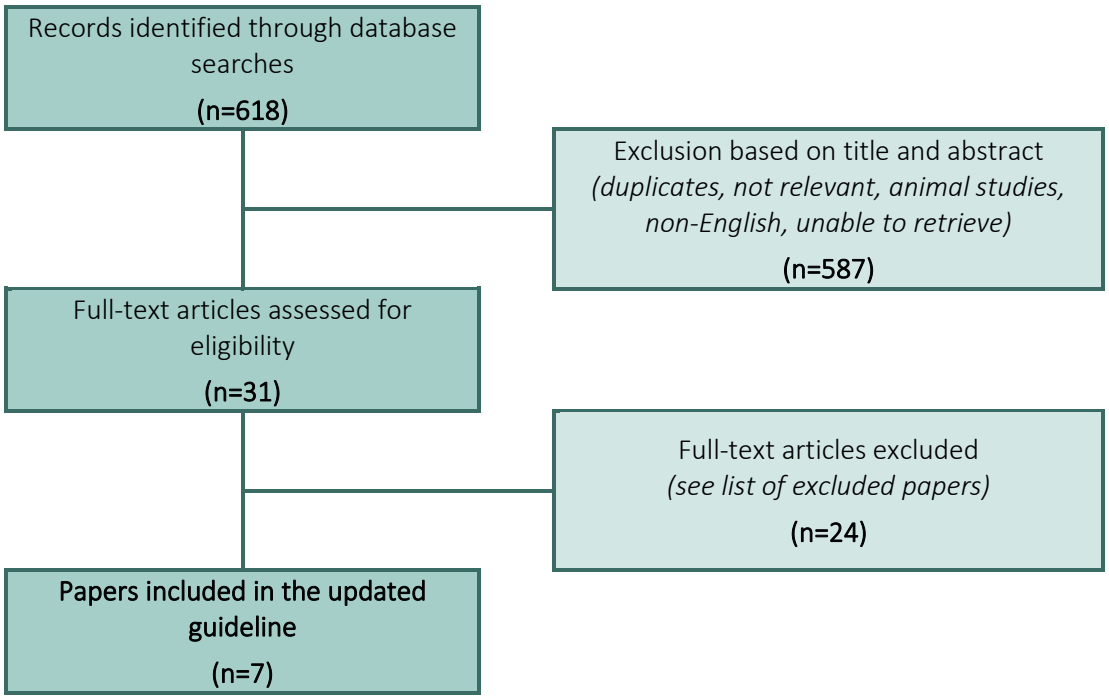


List of excluded papers

	EXCLUSION CRITERIA
Elsharkawy, et al., Effect of Happiness Counseling on Depression, Anxiety, and Stress in Women with Recurrent Miscarriage. Int J Womens Health, 2021. 13: p. 287-295.	This study does not provide materially data different as in the 2017 guideline
Tavoli, et al., Quality of life and psychological distress in women with recurrent miscarriage: a comparative study. Health Qual Life Outcomes, 2018. 16(1): p. 150.	This study does not provide materially data different as in the 2017 guideline
Koert, et al., Recurrent pregnancy loss: couples' perspectives on their need for treatment, support and follow up. Hum Reprod, 2019. 34(2): p. 291-296.	Small sample size
Bailey, et al., Hope for the best …but expect the worst: a qualitative study to explore how women with recurrent miscarriage experience the early waiting period of a new pregnancy. BMJ Open, 2019. 9(5): p. e029354.	Small sample size

2. What are the known risk factors of RPL?

Flowchart


Records identified through database searches
(n=618)
Exclusion based on title and abstract
(duplicates, not relevant, animal studies, non-English, unable to retrieve)
(n=587)
Full-text articles assessed for eligibility
(n=31)
Full-text articles excluded
(see list of excluded papers)
(n=24)
Papers included in the updated guideline
(n=7)

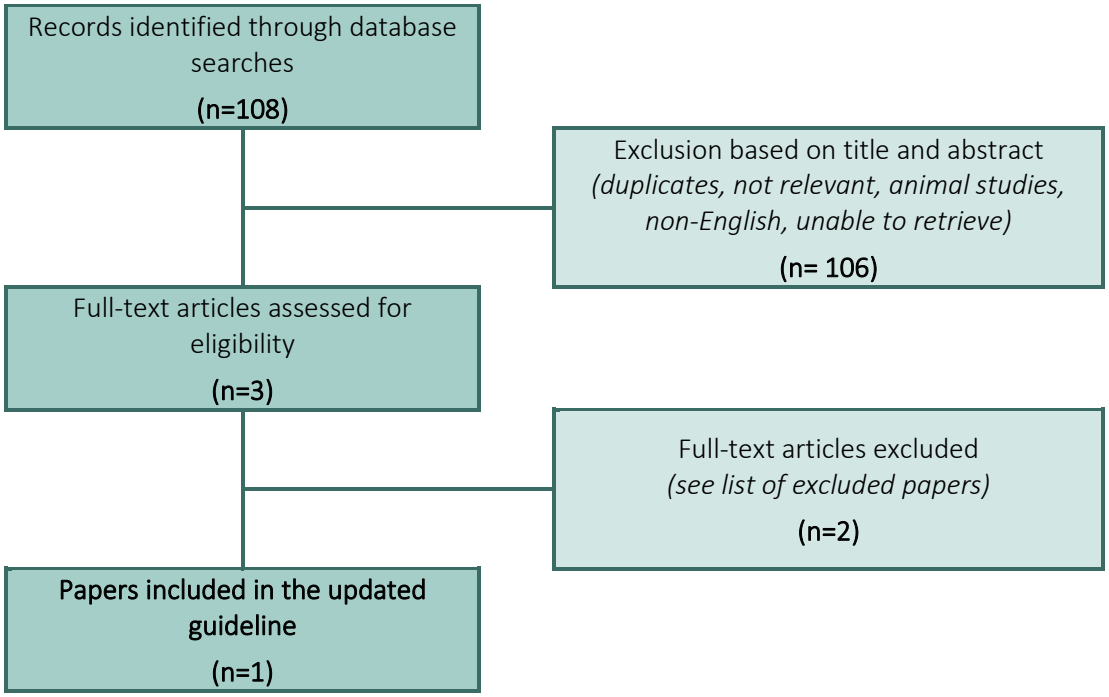
List of excluded papers

	EXCLUSION CRITERION
Cavalcante, et al., Obesity and recurrent miscarriage: A systematic review and meta-analysis. J Obstet Gynaecol Res, 2019. 45(1): p. 30-38.	Not relevant for this question.
Rehman, et al., Unpasteurised milk consumption as a potential risk factor for toxoplasmosis in females with recurrent pregnancy loss. J Obstet Gynaecol, 2020. 40(8): p. 1106-1110.	Not relevant for this question
Fan, et al., The alteration and potential relationship of vaginal microbiota and chemokines for unexplained recurrent spontaneous abortion. Medicine (Baltimore), 2020. 99(51): p. e23558.	Not relevant for this question
Zhang, et al., Alteration of vaginal microbiota in patients with unexplained recurrent miscarriage. Exp Ther Med, 2019. 17(5): p. 3307-3316.	This study does not provide materially different data as in the 2017 guideline
Woolner, et al., Family history and risk of miscarriage: A systematic review and meta-analysis of observational studies. Acta Obstet Gynecol Scand, 2020. 99(12): p. 1584-1594.	This systematic review does not provide materially different data as in the 2017 guideline
van Dijk, et al., Recurrent pregnancy loss: diagnostic workup after two or three pregnancy losses? A systematic review of the literature and meta-analysis. Hum Reprod Update, 2020. 26(3): p. 356-367.	Not relevant for this question
Tan, et al., Association between sperm DNA fragmentation and idiopathic recurrent pregnancy loss: a systematic review and meta-analysis. Reprod Biomed Online, 2019. 38(6): p. 951-960.	Not relevant for this question.
McQueen, et al., Sperm DNA fragmentation and recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril, 2019. 112(1): p. 54-60.e3.	Not relevant for this question. Included in question 10
Elsharkawy, et al., Effect of Happiness Counseling on Depression, Anxiety, and Stress in Women with Recurrent Miscarriage. Int J Womens Health, 2021. 13: p. 287-295.	This study does not provide materially different data as in the 2017 guideline
Nazari, et al., Comparison between sperm parameters and chromatin in recurrent pregnancy loss couples after antioxidant therapy. J Family Med Prim Care, 2020. 9(2): p. 597-601.	Not relevant for this question
Wald, et al., High incidence of diminished ovarian reserve in young unexplained recurrent pregnancy loss patients (). Gynecol Endocrinol, 2020. p. 1-3.	Not relevant for this question
Mohanty, et al., Proteomic Signatures in Spermatozoa Reveal the Role of Paternal Factors in Recurrent Pregnancy Loss. World J Mens Health, 2020. 38(1): p. 103-114.	Not relevant for the update of the guideline
Miyaji, et al., Clinical factors associated with pregnancy outcome in women with recurrent pregnancy loss. Gynecol Endocrinol, 2019. 35(10): p. 913-918.	Not relevant for the update of the guideline
Onat, et al., Telomere Length in Idiopathic Recurrent Pregnancy Loss. Z Geburtshilfe Neonatol, 2021. p.	Not relevant for the update of the guideline
Zhu, et al., Sperm DNA fragmentation in Chinese couples with unexplained recurrent pregnancy loss. Asian J Androl, 2020. 22(3): p. 296-301.	Not relevant for this question. Included in question 9.
Youssef, et al., Defining recurrent pregnancy loss: associated factors and prognosis in couples with two versus three or more pregnancy losses. Reprod Biomed Online, 2020. 41(4): p. 679-685.	Not relevant for this question. Included in question 2
Ribas-Maynou, et al., Sperm chromatin condensation and single- and double-stranded DNA damage as important parameters to	Not relevant for the update of the guideline

define male factor related recurrent miscarriage. Mol Reprod Dev, 2020. 87(11): p. 1126-1132.	
Mayrhofer, et al., The Prevalence and Impact of Polycystic Ovary Syndrome in Recurrent Miscarriage: A Retrospective Cohort Study and Meta-Analysis. J Clin Med, 2020. 9(9): p.	Not relevant for this question
Chen, et al., Stress, anxiety and depression perceived by couples with recurrent miscarriage. Int J Nurs Pract, 2020. 26(2): p. e12796.	Small sample size
Bashiri, et al., A proposed prognostic prediction tool for a live birth among women with recurrent pregnancy loss. J Matern Fetal Neonatal Med, 2020. p. 1-7.	Not relevant for this question. Included in question 10
Ali, et al., Evaluation of etiology and pregnancy outcome in recurrent miscarriage patients. Saudi J Biol Sci, 2020. 27(10): p. 2809-2817.	Irrelevant for guideline update
Ali, et al., Impact of Recurrent Miscarriage on Maternal Outcomes in Subsequent Pregnancy: The Mutaba'ah Study. Int J Womens Health, 2020. 12: p. 1171-1179.	This study does not provide materially different data as in the 2017 guideline
Yuan, et al., Sperm DNA fragmentation valued by SCSA and its correlation with conventional sperm parameters in male partner of recurrent spontaneous abortion couple. Biosci Trends, 2019. 13(2): p. 152-159.	Irrelevant for guideline update
Prasad, et al., Cytokine-induced expression of nitric oxide synthases in Chlamydia trachomatis-infected spontaneous aborters. J Matern Fetal Neonatal Med, 2019. 32(21): p. 3511-3519.	Not relevant for this question
Kolte, et al., Pregnancy outcomes after recurrent pregnancy loss: a longitudinal cohort study on stress and depression. Reprod Biomed Online, 2019. 38(4): p. 599-605.	Not relevant for this question. Included in question 3
Jayasena, et al., Reduced Testicular Steroidogenesis and Increased Semen Oxidative Stress in Male Partners as Novel Markers of Recurrent Miscarriage. Clin Chem, 2019. 65(1): p. 161-169.	Not relevant for the update of the guideline
Tavoli, et al., Quality of life and psychological distress in women with recurrent miscarriage: a comparative study. Health Qual Life Outcomes, 2018. 16(1): p. 150.	This study does not provide materially different data as in the 2017 guideline

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

Flowchart

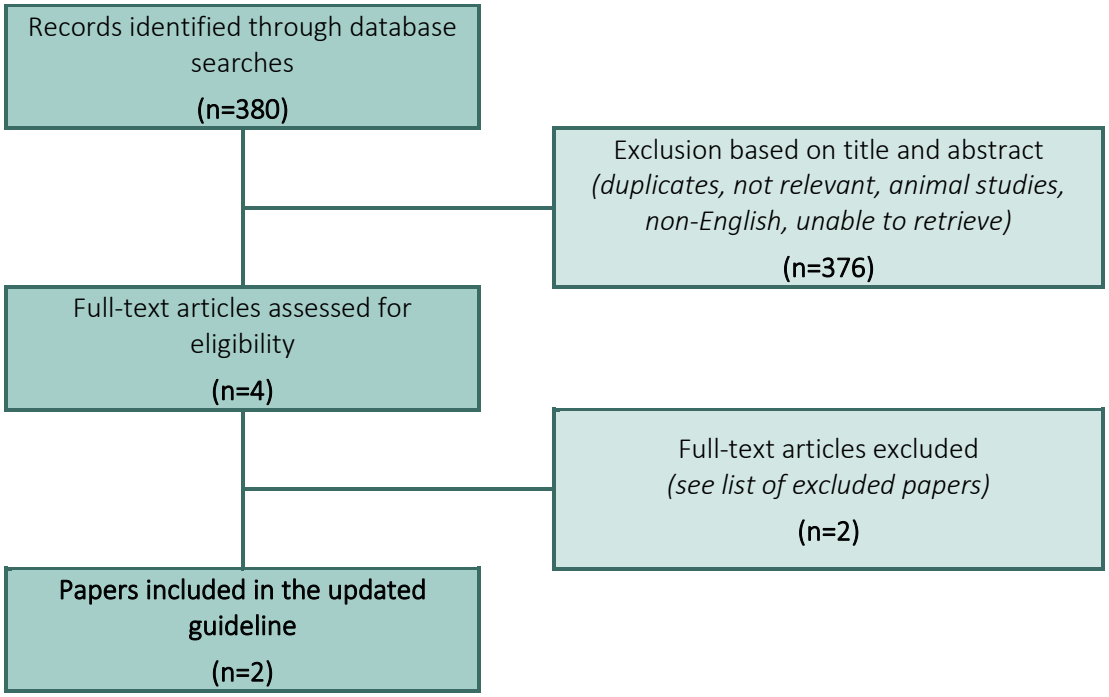


List of excluded papers

	EXCLUSION CRITERION
Cavalcante, et al., Obesity and recurrent miscarriage: A systematic review and meta-analysis. J Obstet Gynaecol Res, 2019. 45(1): p. 30-38.	This systematic review does not provide materially different data as in the 2017 guideline
Vahid, et al., Association between Maternal Dietary Inflammatory Index (DII) and abortion in Iranian women and validation of DII with serum concentration of inflammatory factors: case-control study. Appl Physiol Nutr Metab, 2017. 42(5): p. 511-516.	Not RPL

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

Flowchart

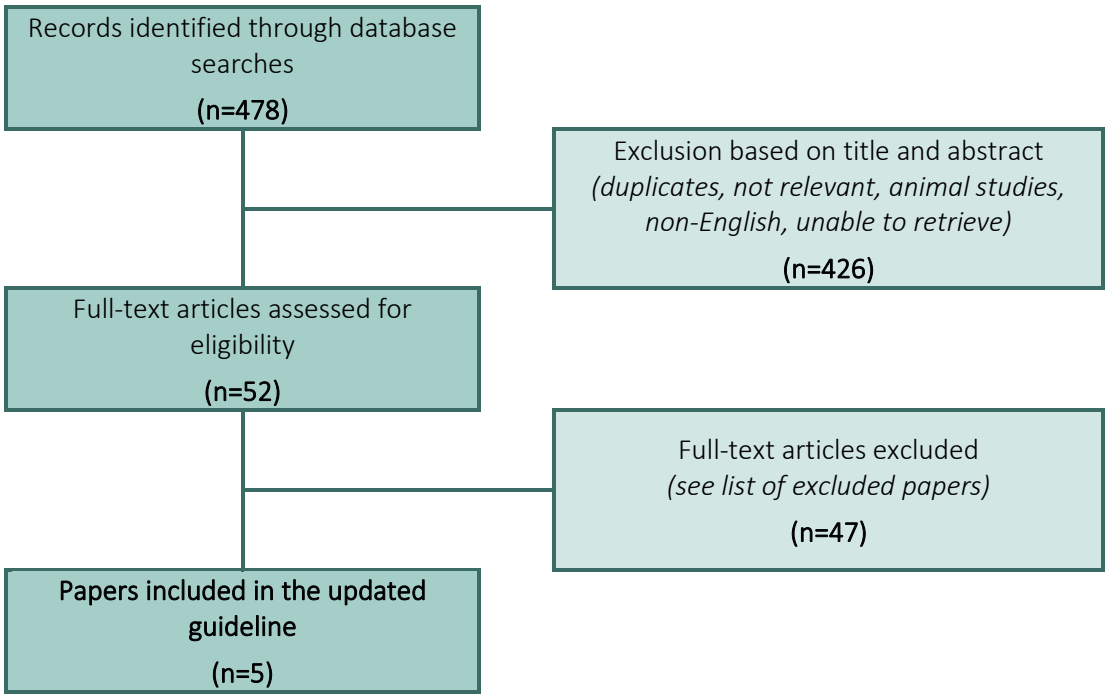


List of excluded papers

	EXCLUSION CRITERIA
Woolner, et al., Family history and risk of miscarriage: A systematic review and meta-analysis of observational studies. Acta Obstet Gynecol Scand, 2020. 99(12): p. 1584-1594.	This systematic review does not provide materially different data as in the 2017 guideline
Wang, et al., Predictive value of thromboelastography parameters combined with antithrombin III and D-Dimer in patients with recurrent spontaneous abortion. Am J Reprod Immunol, 2019. 82(4): p. e13165.	Not relevant for the update of the guideline

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

Flowchart



List of excluded papers

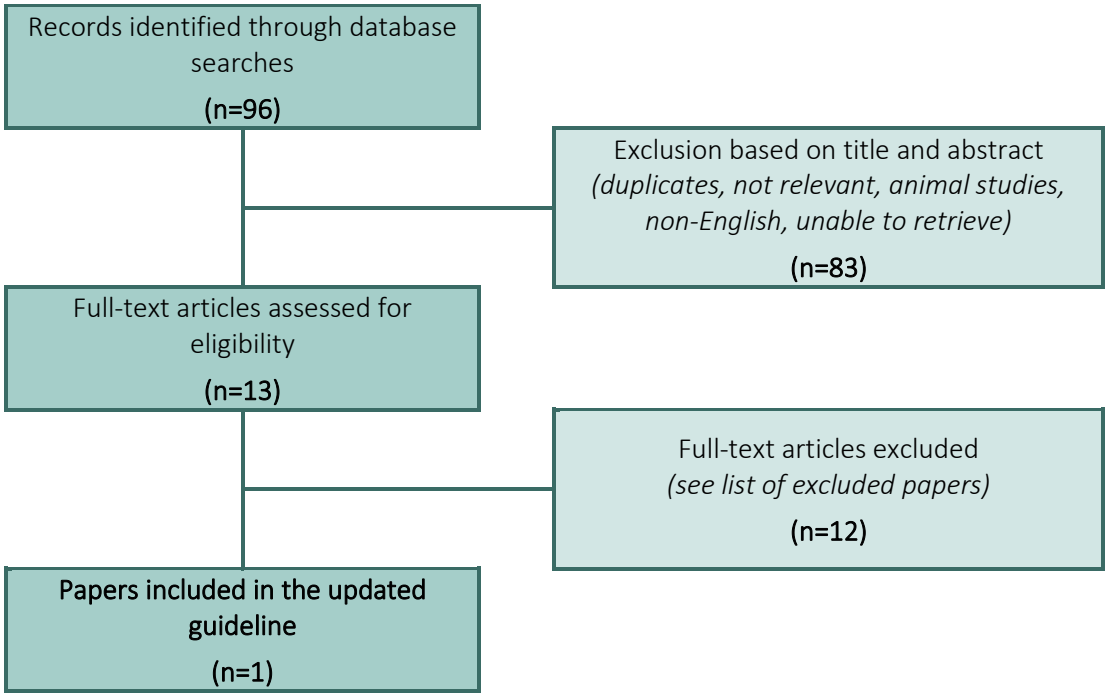
	EXCLUSION CRITERIA
Blue, et al., Genetic abnormalities and pregnancy loss. Semin Perinatol, 2019. 43(2): p. 66-73.	Narrative review
Papas and Kutteh, A new algorithm for the evaluation of recurrent pregnancy loss redefining unexplained miscarriage: review of current guidelines. Curr Opin Obstet Gynecol, 2020. 32(5): p. 371-379.	Non-systematic review
Moghbeli, Genetics of recurrent pregnancy loss among Iranian population. Mol Genet Genomic Med, 2019. 7(9): p. e891.	Non-systematic review
Khalife, et al., Review of current guidelines for recurrent pregnancy loss: new strategies for optimal evaluation of women who may be superfertile. Semin Perinatol, 2019. 43(2): p. 105-115.	Non-systematic review
Kaser, The Status of Genetic Screening in Recurrent Pregnancy Loss. Obstet Gynecol Clin North Am, 2018. 45(1): p. 143-154.	Narrative review
Sheng, et al., Characterization of Copy-Number Variations and Possible Candidate Genes in Recurrent Pregnancy Losses. Genes (Basel), 2021. 12(2): p.	This study is not relevant for the update of the guideline
Li, et al., RNA Sequencing of Decidua Reveals Differentially Expressed Genes in Recurrent Pregnancy Loss. Reprod Sci, 2021. p.	Small sample size
Feng, et al., Acrocentric Chromosome Polymorphic Variants on Chinese Female Have Possible Association with Unexplained Recurrent Pregnancy Loss. Reprod Sci, 2021. 28(2): p. 575-584.	Not relevant for the update of the guidleine
Zhou, et al., Clinical Utility of a High-Resolution Melting Test for Screening Numerical Chromosomal Abnormalities in Recurrent Pregnancy Loss. J Mol Diagn, 2020. 22(4): p. 523-531.	Not relevant for the update of the guideline
Wang, et al., Cytogenetic and genetic investigation of miscarriage cases in Eastern China. J Matern Fetal Neonatal Med, 2020. 33(20): p. 3385-3390.	Not relevant for the update of the guideline
Visconti, et al., Recurrent miscarriage and fetal congenital malformations: Is there a neglected causal association? Eur J Obstet Gynecol Reprod Biol, 2020. 248: p. 233-237.	RPL women as small size subpopulation
Poornima, et al., Chromosomal Abnormalities in Couples with Primary and Secondary Infertility: Genetic Counseling for Assisted Reproductive Techniques (ART). J Reprod Infertil, 2020. 21(4): p. 269-274.	Not relevant for the update of the guideline
Pi, et al., DNA methylation profiling in recurrent miscarriage. PeerJ, 2020. 8: p. e8196.	Not relevant for this question.
Nikitina, et al., Karyotype evaluation of repeated abortions in primary and secondary recurrent pregnancy loss. J Assist Reprod Genet, 2020. 37(3): p. 517-525.	Comparison of primary and secondary RPL
Maddirevula, et al., A genomics approach to females with infertility and recurrent pregnancy loss. Hum Genet, 2020. 139(5): p. 605-613.	Specific gene polymorphism
Gomez, et al., Genetic findings in miscarriages and their relation to the number of previous miscarriages. Arch Gynecol Obstet, 2020. p.	Mixed population RPL and spontaneaous abortion.
Elhady, et al., Chromosomal Aberrations in 224 Couples with Recurrent Pregnancy Loss. J Hum Reprod Sci, 2020. 13(4): p. 340-348.	No control group
Cavalcante, et al., Cytogenetic abnormalities in couples with a history of primary and secondary recurrent miscarriage: a Brazilian Multicentric Study. J Matern Fetal Neonatal Med, 2020. 33(3): p. 442-448.	Comparison of primary and secondary RPL

Bilibio, et al., Causes of recurrent miscarriage after spontaneous pregnancy and after in vitro fertilization. Am J Reprod Immunol, 2020. 83(5): p. e13226.	Small size study
Bhatt and Agarwal, Study of Spectrum of Chromosomal Rearrangements in Recurrent Pregnancy Loss. J Obstet Gynaecol India, 2020. 70(3): p. 189-194.	No comparison to a control group
Bashiri, et al., A proposed prognostic prediction tool for a live birth among women with recurrent pregnancy loss. J Matern Fetal Neonatal Med, 2020. p. 1-7.	Not relevant for this question. Included in question 10
Atefvahid, et al., Copy number variations in miscarriage products and their relationship with consanguinity and recurrent miscarriage in individuals with normal karyotypes. Mol Cell Probes, 2020. 51: p. 101526.	No relevant population
Alibakhshi, et al., Cytogenetic Analysis of 570 Couples with Recurrent Pregnancy Loss: Reporting 11 Years of Experience. J Hum Reprod Sci, 2020. 13(3): p. 216-220.	No control group
Yildirim, et al., The type and prevalence of chromosomal abnormalities in couples with recurrent first trimester abortions: A Turkish retrospective study. J Gynecol Obstet Hum Reprod, 2019. 48(7): p. 521-525.	Low number of patients and no control group
Sato, et al., Analysis of chromosome microstructures in products of conception associated with recurrent miscarriage. Reprod Biomed Online, 2019. 38(5): p. 787-795.	Small sample size
Sak, et al., Cytogenetic screening in couples with Habitual Abortions. J Gynecol Obstet Hum Reprod, 2019. 48(3): p. 155-158.	No control group
Morita, et al., Risk Factors and Outcomes of Recurrent Pregnancy Loss in Japan. J Obstet Gynaecol Res, 2019. 45(10): p. 1997-2006.	Not relevant population
Lovrečić, et al., Combination of QF-PCR and aCGH is an efficient diagnostic strategy for the detection of chromosome aberrations in recurrent miscarriage. Mol Genet Genomic Med, 2019. 7(12): p. e980.	Not relevant for the update of the guideline
Elkarhat, et al., Chromosomal abnormalities in couples with recurrent spontaneous miscarriage: a 21-year retrospective study, a report of a novel insertion, and a literature review. J Assist Reprod Genet, 2019. 36(3): p. 499-507.	Not relevant for the update of the guideline
Du, et al., The Possible Involvement of miR-371a-5p Regulating XIAP in the Pathogenesis of Recurrent Pregnancy Loss. Reprod Sci, 2019. 26(11): p. 1468-1475.	miRNA expression
Dong, et al., Genome Sequencing Explores Complexity of Chromosomal Abnormalities in Recurrent Miscarriage. Am J Hum Genet, 2019. 105(6): p. 1102-1111.	This study does not provide materially different material as in the 2017 guideline
Priya, et al., A Study on Balanced Chromosomal Translocations in Couples with Recurrent Pregnancy Loss. J Hum Reprod Sci, 2018. 11(4): p. 337-342.	This study does not provide materially different material as in the 2017 guideline
Pal, et al., Chromosomal Aberrations in Couples with Pregnancy Loss: A Retrospective Study. J Hum Reprod Sci, 2018. 11(3): p. 247-253.	This study does not provide materially different data as in the 2017 guideline
Kabessa, et al., Pregnancy outcomes among patients with recurrent pregnancy loss and chromosomal aberration (CA) without PGD. J Perinat Med, 2018. 46(7): p. 764-770.	Small sample size and selection bias
Hajlaoui, et al., Subtelomeric Rearrangements in Patients with Recurrent Miscarriage. Int J Fertil Steril, 2018. 12(3): p. 218-222.	Not relevant for the update if the guideline
Feichtinger, et al., Embryoscopy and karyotype findings of repeated miscarriages in recurrent pregnancy loss and spontaneous pregnancy loss. J Assist Reprod Genet, 2018. 35(8): p. 1401-1406.	RPL women as small size subpopualtion

Du, et al., Chromosomal karyotype in chorionic villi of recurrent spontaneous abortion patients. Biosci Trends, 2018. 12(1): p. 32-39.	Not relevant for the update of the guideline
Dobson and Jayaprakasan, Aetiology of recurrent miscarriage and the role of adjuvant treatment in its management: a retrospective cohort review. J Obstet Gynaecol, 2018. 38(7): p. 967-974.	Non-systematic review
Azadi, et al., Mitochondrial DNA variations are associated with recurrent pregnancy loss. Mitochondrial DNA A DNA Mapp Seq Anal, 2018. 29(5): p. 674-678.	Small sample size
Awartani and Al Shabibi, Description of cytogenetic abnormalities and the pregnancy outcomes of couples with recurrent pregnancy loss in a tertiary-care center in Saudi Arabia. Saudi Med J, 2018. 39(3): p. 239-242.	This study does not provide materially different data as in the 2017 guideline
Wu, et al., Role of peroxiredoxin2 downregulation in recurrent miscarriage through regulation of trophoblast proliferation and apoptosis. Cell Death Dis, 2017. 8(6): p. e2908.	Not relevant for the update of the guideline
Quintero-Ronderos, et al., Novel genes and mutations in patients affected by recurrent pregnancy loss. PLoS One, 2017. 12(10): p. e0186149.	Not relevant for the update of the guidleine
Karim, et al., Genomic answers for recurrent spontaneous abortion in Saudi Arabia: An array comparative genomic hybridization approach. Reprod Biol, 2017. 17(2): p. 133-143.	Not relevant for the update pf the guideline
Ayed, et al., Chromosomal abnormalities in 163 Tunisian couples with recurrent miscarriages. Pan Afr Med J, 2017. 28: p. 99.	Not relevant for the update of the guideline
Klimczak, et al., Role of the sperm, oocyte, and embryo in recurrent pregnancy loss. Fertil Steril, 2021. 115(3): p. 533-537.	Narrative review
Zhang, et al., Traditional and molecular chromosomal abnormality analysis of products of conception in spontaneous and recurrent miscarriage. Bjog, 2018. 125(4): p. 414-420.	Narrative review
Hong Li and Marren, Recurrent pregnancy loss: A summary of international evidence-based guidelines and practice. Aust J Gen Pract, 2018. 47(7): p. 432-436.	Non-systematic review

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

Flowchart

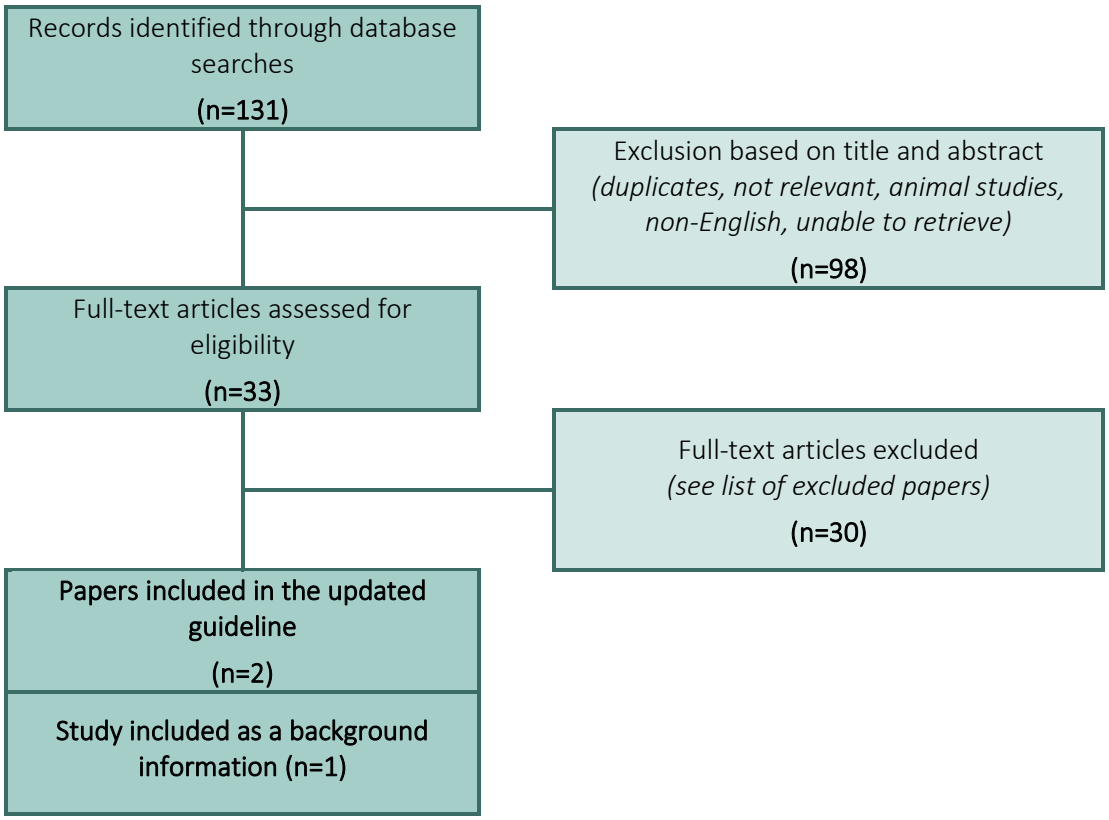


List of excluded papers

	EXCLUSION CRITERIA
Liu, et al., Hereditary thrombophilia and recurrent pregnancy loss: a systematic review and meta-analysis. Hum. Reprod, 2021. P.	This systematic review does not provide materially different data as in the 2017 guideline; Their suggestion to test is not based on the data.
Han, et al., Inherited thrombophilia and anticoagulant therapy for women with reproductive failure. Am J Reprod Immunol, 2020. p. e13378.	
van Dijk, et al., Recurrent pregnancy loss: diagnostic workup after two or three pregnancy losses? A systematic review of the literature and meta-analysis. Hum Reprod Update, 2020. 26(3): p. 356-367.	This systematic review does not provide materially different data as in the 2017 guideline
Zhang, et al., The association between maternal methylenetetrahydrofolate reductase C677T and A1298C polymorphism and birth defects and adverse pregnancy outcomes. Prenat Diagn, 2019. 39(1): p. 3-9.	Specic gene polymorphism
Tanimura, et al., The β(2) -Glycoprotein I/HLA-DR Complex As A Major Autoantibody Target in Obstetric Antiphospholipid Syndrome. Arthritis Rheumatol, 2020. p.	This study does not provide materially different data as in the 2017 guideline
Wang, et al., Predictive value of thromboelastography parameters combined with antithrombin III and D-Dimer in patients with recurrent spontaneous abortion. Am J Reprod Immunol, 2019. 82(4): p. e13165.	Results cannot be generalized. Only women with RPL at less than 10 weeks of gestation were included
Mishra, et al., Differential global and MTHFR gene specific methylation patterns in preeclampsia and recurrent miscarriages: A case-control study from North India. Gene, 2019. 704: p. 68-73.	Small sample size
Abd Al-Badri and Abdul-Hassan, Serum total homocysteine level in Iraqi woman with unexplained recurrent Miscarriage. J Pak Med Assoc, 2019. 69(Suppl 3)(8): p. S26-s30.	Small sample size
Nahas, et al., The Prevalence of Thrombophilia in Women With Recurrent Fetal Loss and Outcome of Anticoagulation Therapy for the Prevention of Miscarriages. Clin Appl Thromb Hemost, 2018. 24(1): p. 122-128.	RPL women are a subpopulation
Barut, et al., Thrombophilia and Recurrent Pregnancy Loss: The Enigma Continues. Med Sci Monit, 2018. 24: p. 4288-4294.	This study is a single-centre study from a single private hospital. It does not provide materially different data as in the 2017 guideline
Wang, et al., Prediction of thrombophilia in patients with unexplained recurrent pregnancy loss using a statistical model. Int J Gynaecol Obstet, 2017. 138(3): p. 283-287.	Not relevant for this question
Hwang, et al., Methylenetetrahydrofolate Reductase Polymorphisms and Risk of Recurrent Pregnancy Loss: a Case-Control Study. J Korean Med Sci, 2017. 32(12): p. 2029-2034.	Not relevant for the update of the guideline

7. What is the value of immunological screening in the diagnosis of RPL? (including aim and indications) (6)

Flowchart



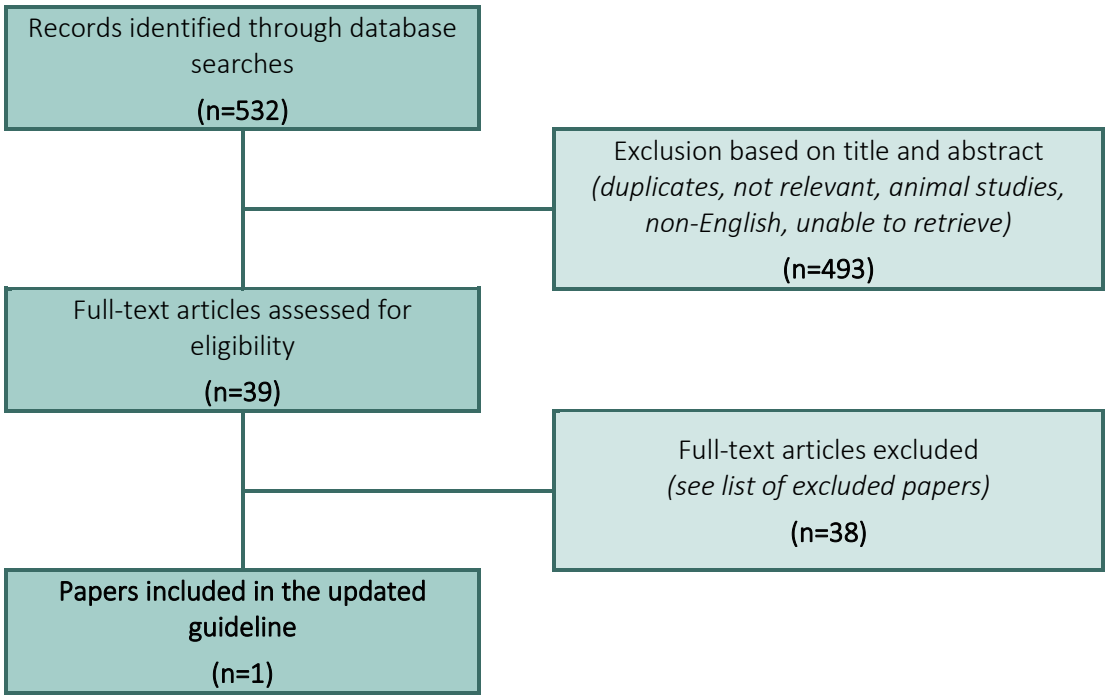
List of excluded papers

	EXCLUSION CRITERIA
Cavalcante, et al., Antinuclear antibodies and recurrent miscarriage: Systematic review and meta-analysis. Am J Reprod Immunol, 2020. 83(3): p. e13215.	Same conclusions as the Chen meta-analysis
Bruno, et al., Uterine and placental blood flow indexes and antinuclear autoantibodies in unexplained recurrent pregnancy loss: should they be investigated in pregnancy as correlated potential factors? A retrospective study. BMC Pregnancy Childbirth, 2020. 20(1): p. 44.	Not very informative
Hefler-Frischmuth, et al., Serologic markers of autoimmunity in women with recurrent pregnancy loss. Am J Reprod Immunol, 2017. 77(4): p.	Uses ELISA technique which is uncommon for ANA detection
D'Ippolito, et al., The pathogenic role of autoantibodies in recurrent pregnancy loss. Am J Reprod Immunol, 2020. 83(1): p. e13200.	Narrative review
Lyzikova, et al., Increase in FoxP3, CD56 immune cells and decrease in glands PGRMC1 expression in the endometrium are associated with recurrent miscarriages. Eur J Obstet Gynecol Reprod Biol, 2020. 245: p. 121-126.	Not relevant for the update of the guideline
Freitag, et al., Are uterine natural killer and plasma cells in infertility patients associated with endometriosis, repeated implantation failure, or recurrent pregnancy loss? Arch Gynecol Obstet, 2020. 302(6): p. 1487-1494.	Small sample size of women with RPL
Sokolov, et al., NK and trophoblast cells interaction: cytotoxic activity on recurrent pregnancy loss. Gynecol Endocrinol, 2019. 35(sup1): p. 5-10.	Small sample size
El-Azzamy, et al., Dysregulated uterine natural killer cells and vascular remodeling in women with recurrent pregnancy losses. Am J Reprod Immunol, 2018. 80(4): p. e13024.	Small sample size
Chen, et al., Increased expression of angiogenic cytokines in CD56+ uterine natural killer cells from women with recurrent miscarriage. Cytokine, 2018. 110: p. 272-276.	Not clinically relevant
Adib Rad, et al., Evaluation of peripheral blood NK cell subsets and cytokines in unexplained recurrent miscarriage. J Chin Med Assoc, 2018. 81(12): p. 1065-1070.	Not clinically relevant
Zhu, et al., Decreased NK cell immunity in kidney transplant recipients late post-transplant and increased NK-cell immunity in patients with recurrent miscarriage. PLoS One, 2017. 12(10): p. e0186349.	Two very different groups compared, no clinical useful information
Kuon, et al., Uterine natural killer cells in patients with idiopathic recurrent miscarriage. Am J Reprod Immunol, 2017. 78(4): p.	This study does not provide materially different data as in the 2017 guideline
Kuon, et al., The "killer cell story" in recurrent miscarriage: Association between activated peripheral lymphocytes and uterine natural killer cells. J Reprod Immunol, 2017. 119: p. 9-14.	Not relevant for th update of the guideline
Kolanska, et al., Proportion of Cytotoxic Peripheral Blood Natural Killer Cells and T-Cell Large Granular Lymphocytes in Recurrent Miscarriage and Repeated Implantation Failure: Case-Control Study and Meta-analysis. Arch Immunol Ther Exp (Warsz), 2019. 67(4): p. 225-236.	This meta-analysis does not provide materiallay different data as in the 2017 guideline
Zhu, et al., Patients with idiopathic recurrent miscarriage have abnormally high TGFß+ blood NK, NKT and T cells in the presence of abnormally low TGFß plasma levels. BMC Immunol, 2019. 20(1): p. 10.	Not relevant for the update of the guidleine

Fukui, et al., Expression of natural cytotoxicity receptors and cytokine production on endometrial natural killer cells in women with recurrent pregnancy loss or implantation failure, and the expression of natural cytotoxicity receptors on peripheral blood natural killer cells in pregnant women with a history of recurrent pregnancy loss. J Obstet Gynaecol Res, 2017. 43(11): p. 1678-1686.	Small sample size
Ebina, et al., Natural killer cell activity in women with recurrent miscarriage: Etiology and pregnancy outcome. J Reprod Immunol, 2017. 120: p. 42-47.	Results were not adajusted for cofounders
Ticconi, et al., Endometrial Immune Dysfunction in Recurrent Pregnancy Loss. Int J Mol Sci, 2019. 20(21): p.	Narrative review
Vomstein, et al., Two of a kind? Immunological and clinical risk factors differ between recurrent implantation failure and recurrent miscarriage. J Reprod Immunol, 2020. 141: p. 103166.	Study comparing RPL and recurrent implantation failure women
Mansour, et al., Association of Killer Immunoglobulin-Like Receptor and Human Leukocyte Antigen Class I Ligand with Recurrent Abortion in Saudi Women. Genet Test Mol Biomarkers, 2020. 24(2): p. 78-84.	Small sample size
Fan, et al., The alteration and potential relationship of vaginal microbiota and chemokines for unexplained recurrent spontaneous abortion. Medicine (Baltimore), 2020. 99(51): p. e23558.	Not relevant for thisq question
Chen, et al., Association between chronic endometritis and uterine natural killer cell density in women with recurrent miscarriage: clinical implications. J Obstet Gynaecol Res, 2020. 46(6): p. 858-863.	This study does not provide materially different data as in the 2017 guideline
Bilibio, et al., Causes of recurrent miscarriage after spontaneous pregnancy and after in vitro fertilization. Am J Reprod Immunol, 2020. 83(5): p. e13226.	This study fonds frequency of ANA increased in RPL after spontaneous conception compared with after IVF. Not very clinically relevant
Basimi, et al., Comparing the Frequency of CD4+T Cells in Recurrent Spontaneous Abortion Women with and without Anti-thyroid Peroxidase (TPO). Iran J Allergy Asthma Immunol, 2020. 19(1): p. 65-73.	Not relevant for this question
Zhu, et al., Detection of non-criteria autoantibodies in women without apparent causes for pregnancy loss. J Clin Lab Anal, 2019. 33(9): p. e22994.	Not relevant for the update of the guideline
Ye, et al., Anti α-enolase antibody is a novel autoimmune biomarker for unexplained recurrent miscarriages. EBioMedicine, 2019. 41: p. 610-622.	No relevant population
Bliddal, et al., Thyroid Peroxidase Antibodies and Prospective Live Birth Rate: A Cohort Study of Women with Recurrent Pregnancy Loss. Thyroid, 2019. 29(10): p. 1465-1474.	Not relevant for this question
Tersigni, et al., Recurrent pregnancy loss is associated to leaky gut: a novel pathogenic model of endometrium inflammation? J Transl Med, 2018. 16(1): p. 102.	Not relevant for the update of the guideline
Wu, et al., Serum biomarker analysis in patients with recurrent spontaneous abortion. Mol Med Rep, 2017. 16(3): p. 2367-2378.	Small sample size
Promberger, et al., A Retrospective Study on the Association between Thyroid Autoantibodies with β2-glycoprotein and Cardiolipin Antibodies in Recurrent Miscarriage. Iran J Allergy Asthma Immunol, 2017. 16(1): p. 72-76.	Not relevant for the update of the guideline

8. What is the value of screening for metabolic/endocrinological abnormalities in the diagnosis of RPL?

Flowchart


Records identified through database searches
(n=532)
Exclusion based on title and abstract
(duplicates, not relevant, animal studies, non-English, unable to retrieve)
(n=493)
Full-text articles assessed for eligibility
(n=39)
Full-text articles excluded
(see list of excluded papers)
(n=38)
Papers included in the updated guideline
(n=1)

List of excluded papers

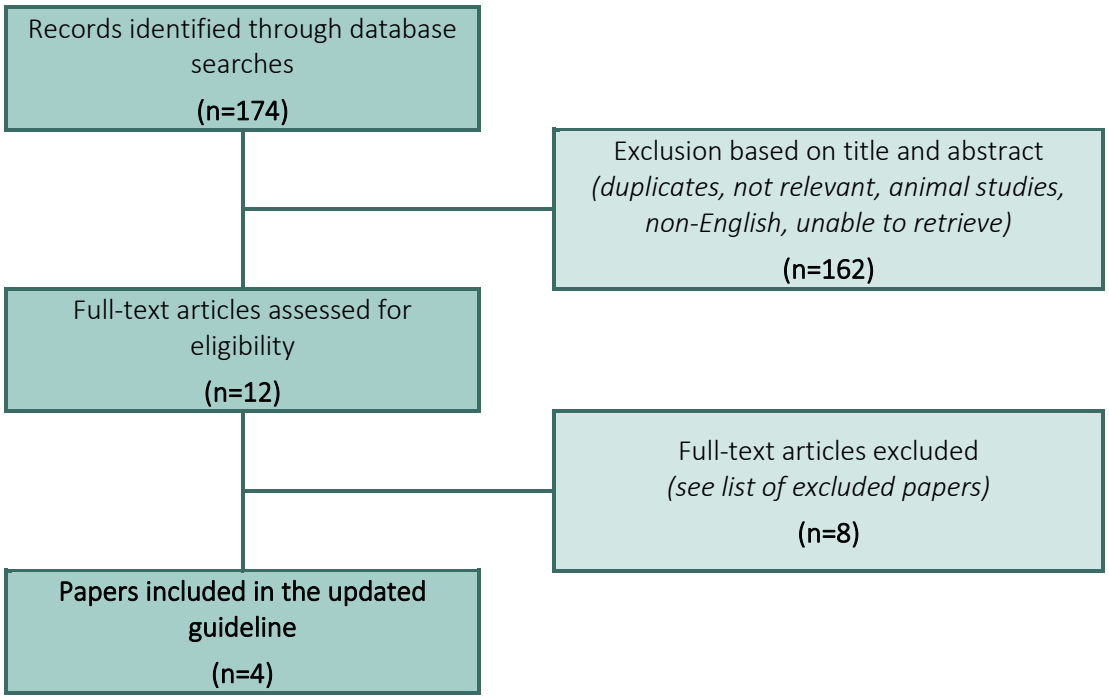
	EXCLUSION CRITERIA
Xie, et al., Effect of antithyroid antibodies on women with recurrent miscarriage: A meta-analysis. Am J Reprod Immunol, 2020. 83(6): p. e13238.	This meta-analysis does not provide materially different data as in the 2017 guideline
Bliddal, et al., Thyroid Peroxidase Antibodies and Prospective Live Birth Rate: A Cohort Study of Women with Recurrent Pregnancy Loss. Thyroid, 2019. 29(10): p. 1465-1474.	Included in the Bunnewell meta-analysis
DiMarco, et al., Undiagnosed Primary Hyperparathyroidism and Recurrent Miscarriage: The First Prospective Pilot Study. World J Surg, 2018. 42(3): p. 639-645.	Pilot study
Promberger, et al., A Retrospective Study on the Association between Thyroid Autoantibodies with β2-glycoprotein and Cardiolipin Antibodies in Recurrent Miscarriage. Iran J Allergy Asthma Immunol, 2017. 16(1): p. 72-76.	Small sample size
Cueva, et al., Maternal antithyroid antibodies and euploid miscarriage in women with recurrent early pregnancy loss. Fertil Steril, 2018. 110(3): p. 452-458.	Small sample size
Amrane and McConnell, Endocrine causes of recurrent pregnancy loss. Semin Perinatol, 2019. 43(2): p. 80-83.	Narrative review
Wald, et al., High incidence of diminished ovarian reserve in young unexplained recurrent pregnancy loss patients. Gynecol Endocrinol, 2020. p. 1-3.	Small sample size, single centre study
Sencan, et al., The role of neopterin and anti-Mullerian hormone in unexplained recurrent pregnancy loss - a case-control study. J Obstet Gynaecol, 2019. 39(7): p. 996-999.	Not relevant for the update of the guidleine
Pils, et al., Does anti-Mullerian hormone predict the outcome of further pregnancies in idiopathic recurrent miscarriage? A retrospective cohort study. Arch Gynecol Obstet, 2019. 299(1): p. 259-265.	Not relevant for the update of the guideline
Murugappan, et al., Antimullerian hormone is a predictor of live birth in patients with recurrent pregnancy loss. Fertil Res Pract, 2019. 5: p. 2.	Not relevant for the update of the guideline
McCormack, et al., Anti-Müllerian hormone levels in recurrent embryonic miscarriage patients are frequently abnormal and may affect pregnancy outcomes. J Obstet Gynaecol, 2019. 39(5): p. 623-627.	Not relevant for the update of the guidleine
Leclercq, et al., Blood anti-Müllerian hormone is a possible determinant of recurrent early miscarriage, yet not conclusive in predicting a further miscarriage. Reprod Biomed Online, 2019. 39(2): p. 304-311.	Not relevant for the update of the guideline
Pils, et al., Anti-Mullerian hormone is linked to the type of early pregnancy loss in idiopathic recurrent miscarriage: a retrospective cohort study. Reprod Biol Endocrinol, 2017. 15(1): p. 60.	Not relevant for the update of the guideline
Ji, et al., The role and mechanism of vitamin D-mediated regulation of Treg/Th17 balance in recurrent pregnancy loss. Am J Reprod Immunol, 2019. 81(6): p. e13112.	Not clinically relevant
Abdollahi, et al., Evaluation of 1,25(OH)2D3 Effects on FOXP3, ROR-γt, GITR, and CTLA-4 Gene Expression in the PBMCs of Vitamin D-Deficient Women with Unexplained Recurrent Pregnancy Loss (URPL). Iran Biomed J, 2020. 24(5): p. 295-305.	Not clinically relevant

Abdollahi, et al., Evaluation of the Effects of 1,25 Vitamin D3 on Regulatory T Cells and T Helper 17 Cells in Vitamin D-deficient Women with Unexplained Recurrent Pregnancy Loss. Curr Mol Pharmacol, 2020. 13(4): p. 306-317.	Not clinically relevant
Pei, et al., Pathogenetic factors involved in recurrent pregnancy loss from multiple aspects. Obstet Gynecol Sci, 2019. 62(4): p. 212-223.	Narrative review
Sharif, et al., Vitamin D, autoimmunity and recurrent pregnancy loss: More than an association. Am J Reprod Immunol, 2018. 80(3): p. e12991.	Not relevant for guideline update
Gonçalves, et al., Recurrent pregnancy loss and vitamin D: A review of the literature. Am J Reprod Immunol, 2018. 80(5): p. e13022.	Not relevant for the guideline
Li, et al., Women with recurrent spontaneous abortion have decreased 25(OH) vitamin D and VDR at the fetal-maternal interface. Braz J Med Biol Res, 2017. 50(11): p. e6527.	Not relevant for the guideline
Egerup, et al., Pregnancy loss is associated with type 2 diabetes: a nationwide case-control study. Diabetologia, 2020. 63(8): p. 1521-1529.	Big study on the risk to develop diabetes type 2 after RPL. This forms no evidence to recommend to screen for type 2 diabetes at intake.
Onat, et al., Telomere Length in Idiopathic Recurrent Pregnancy Loss. Z Geburtshilfe Neonatol, 2021. p.	Irrelevant for guideline update
Ali, et al., Evaluation of etiology and pregnancy outcome in recurrent miscarriage patients. Saudi J Biol Sci, 2020. 27(10): p. 2809-2817.	Irrelevant for guideline update
Godines-Enriquez, et al., Prevalence of Thyroid Autoimmunity in Women with Recurrent Pregnancy Loss. Medicina (Kaunas), 2021. 57(2): p.	Irrelevant for this question
McCormack, et al., Do raised two-hour pre-pregnancy insulin levels confer the same risks of developing GDM, as raised fasting levels, in recurrent miscarriage patients? J Obstet Gynaecol, 2020. 40(6): p. 803-807.	Irrelevant for guideline update
Manning, et al., Are we managing women with Recurrent Miscarriage appropriately? A snapshot survey of clinical practice within the United Kingdom. J Obstet Gynaecol, 2020. p. 1-8.	Not relevant for this question
Hilali, et al., Recurrent pregnancy loss and metabolic syndrome. Ginekol Pol, 2020. 91(6): p. 320-323.	Irrelevant for guideline update
Fouani, et al., Circulating levels of Meteorin-like protein in polycystic ovary syndrome: A case-control study. PLoS One, 2020. 15(4): p. e0231943.	Irrelevant for guideline update
Edugbe, et al., Beta-cell dysfunction and abnormal glucose metabolism among non-diabetic women with recurrent miscarriages. Arch Gynecol Obstet, 2020. 301(2): p. 559-564.	Irrelevant for guideline update
Zhang, et al., Liquid Chromatography/Mass Spectrometry based serum metabolomics study on recurrent abortion women with antiphospholipid syndrome. PLoS One, 2019. 14(11): p. e0225463.	Irrelevant for guideline update
Song, et al., Novel high-coverage targeted metabolomics method (SWATHtoMRM) for exploring follicular fluid metabolome alterations in women with recurrent spontaneous abortion undergoing in vitro fertilization. Sci Rep, 2019. 9(1): p. 10873.	Irrelevant for guideline update
Shapiro, et al., Comparison of 2-Hour Oral Glucose Tolerance Test and Hemoglobin A1C in the Identification of Pre-Diabetes in Women with Infertility and Recurrent Pregnancy Loss. Clin Med Insights Reprod Health, 2019. 13: p. 1179558119831280.	Irrelevant for guideline update
Barišić, et al., Genetic variation in the maternal vitamin D receptor FokI gene as a risk factor for recurrent pregnancy loss. J Matern Fetal Neonatal Med, 2019. p. 1-6.	Vit D section, and irrelevant for guideline update

Azizi, et al., Metabolic syndrome mediates inflammatory and oxidative stress responses in patients with recurrent pregnancy loss. J Reprod Immunol, 2019. 133: p. 18-26.	Irrelevant for guideline update
Asanidze, et al.,Correlation between levels of homocysteine, anti-mullerian hormone and insulin resistance in PCOS patients with recurrent miscarriage. Georgian Med News, 2019. (290): p. 25-29.	Irrelevant for guideline update
Kim, et al., Prolactin receptor gene polymorphism and the risk of recurrent pregnancy loss: a case-control study. J Obstet Gynaecol, 2018. 38(2): p. 261-264.	Irrelevant for guideline update
Matjila, et al., Medical conditions associated with recurrent miscarriage-Is BMI the tip of the iceberg? Eur J Obstet Gynecol Reprod Biol, 2017. 214: p. 91-96.	No new advice not already mentioned in guideline (lifestyle).
Dean, et al., Connecting links between genetic factors defining ovarian reserve and recurrent miscarriages. J Assist Reprod Genet, 2018. 35(12): p. 2121-2128.	Irrelevant for the guideline update

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

Flowchart



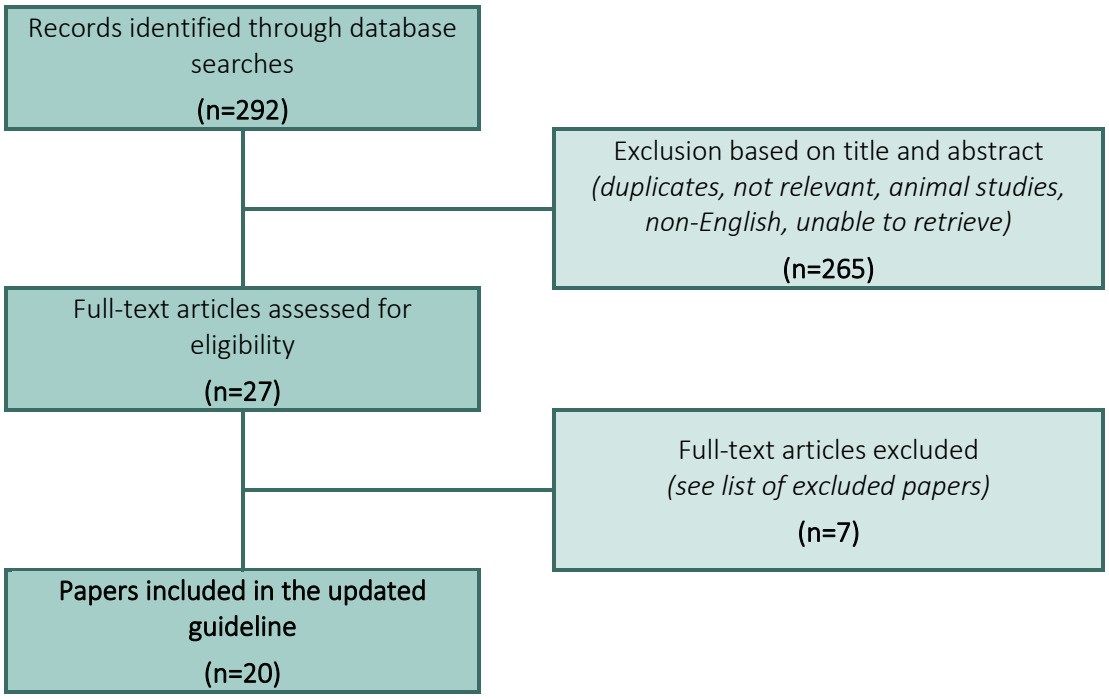
List of excluded papers

	EXCLUSION CRITERIA
Zargar, et al., Evaluating Chronic Endometritis in Women with Recurrent Implantation Failure and Recurrent Pregnancy Loss by Hysteroscopy and Immunohistochemistry. J Minim Invasive Gynecol, 2020. 27(1): p. 116-121.	No control group and study group is small
Atabekoğlu, et al., The association between adenomyosis and recurrent miscarriage. Eur J Obstet Gynecol Reprod Biol, 2020. 250: p. 107-111.	Very small study group
Shiva, et al., Accuracy of Two-Dimensional Transvaginal Sonography and Office Hysteroscopy for Detection of Uterine Abnormalities in Patients with Repeated Implantation Failures or Recurrent Pregnancy Loss. Int J Fertil Steril, 2018. 11(4): p. 287-292.	Not relevant for the guideline update
Sklyarova, et al.,; EPIDEMIOLOGICAL FEATURES OF CHRONIC ENDOMETRITIS IN REPRODUCTIVE AGE WOMEN WITH DISORDERS OF REPRODUCTIVE HEALTH. Georgian Med News, 2020. (304-305): p. 27-32.	Not relevant for the guideline update
Bruno, et al., Uterine and placental blood flow indexes and antinuclear autoantibodies in unexplained recurrent pregnancy loss: should they be investigated in pregnancy as correlated potential factors? A retrospective study. BMC Pregnancy Childbirth, 2020. 20(1): p. 44.	Not relevant for this question
Ali, et al., Evaluation of etiology and pregnancy outcome in recurrent miscarriage patients. Saudi J Biol Sci, 2020. 27(10): p. 2809-2817.	Not relevant for the guideline update

Turocy and Rackow, Uterine factor in recurrent pregnancy loss. Semin Perinatol, 2019. 43(2): p. 74-79.	Not relevant for the guideline update
Manning, et al., Are we managing women with Recurrent Miscarriage appropriately? A snapshot survey of clinical practice within the United Kingdom. J Obstet Gynaecol, 2020. p. 1-8.	Survey not relevant for the guideline update

10. WHAT IS THE VALUE OF MALE SCREENING IN THE DIAGNOSIS OF RPL? (INCLUDING AIM AND INDICATIONS) (9)

Flowchart



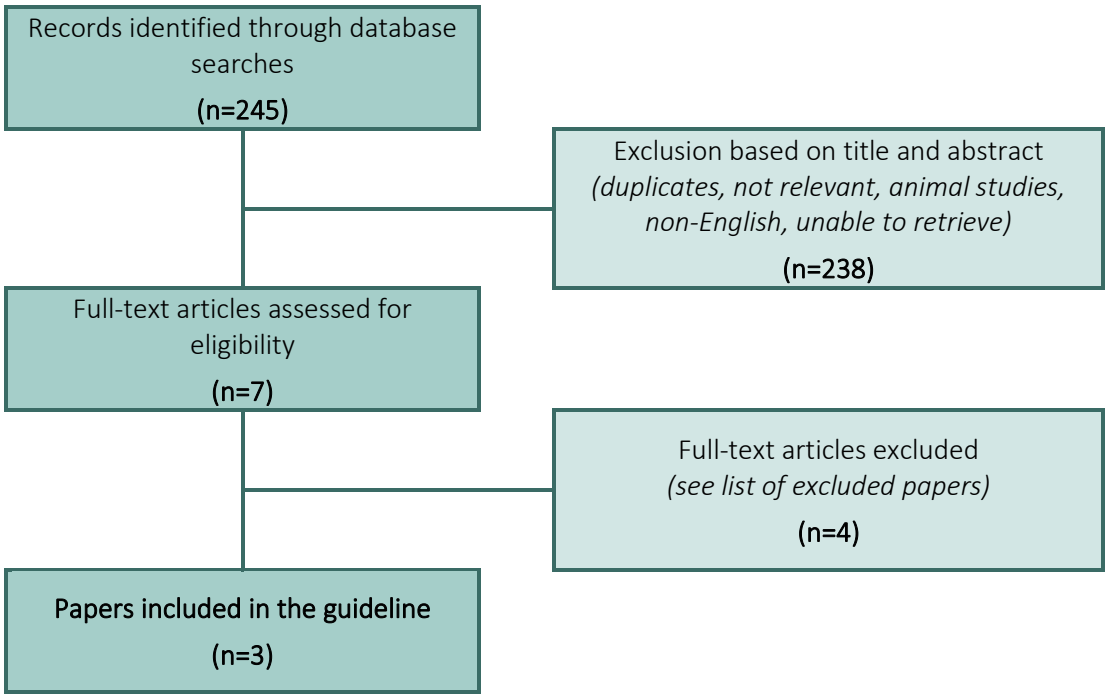
List of excluded papers

	EXCLUSION CRITERIA
Yifu, et al., Sperm DNA fragmentation index with unexplained recurrent spontaneous abortion: A systematic review and meta-analysis. J Gynecol Obstet Hum Reprod, 2020. p. 101740.	This meta-analysis does not provide materially different data as in the 2017 guideline
Sereshki, et al., Decreased Toll-like Receptor (TLR) 2 and 4 Expression in Spermatozoa in Couples with Unexplained Recurrent Spontaneous Abortion (URSA). Iran J Allergy Asthma Immunol, 2019. 18(6): p. 701-706.	This study is not relevant for the update of the guideline
Poorang, et al., The Impact of Methylenetetrahydrofolate Reductase (MTHFR) Sperm Methylation and Variants on Semen Parameters and the Chance of Recurrent Pregnancy Loss in the Couple. Clin Lab, 2018. 64(7): p. 1121-1128.	This study is not relevant for the update of the guideline
Kamkar, et al., The relationship between sperm DNA fragmentation, free radicals and antioxidant capacity with idiopathic repeated pregnancy loss. Reprod Biol, 2018. 18(4): p. 330-335.	This study is not relevant for the update of the guideline
Rogenhofer, et al., Unexplained recurrent miscarriages are associated with an aberrant sperm protamine mRNA content. Hum Reprod, 2017. 32(8): p. 1574-1582.	mRNA expression
Carlini, et al., Sperm DNA fragmentation in Italian couples with recurrent pregnancy loss. Reprod Biomed Online, 2017. 34(1): p. 58-65.	This study does not providematerially different data as in the 2017 guideline

Klimczak, et al., Role of the sperm, oocyte, and embryo in recurrent pregnancy loss. Fertil Steril, 2021. 115(3): p. 533-537.	Narrative review

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

Flowchart

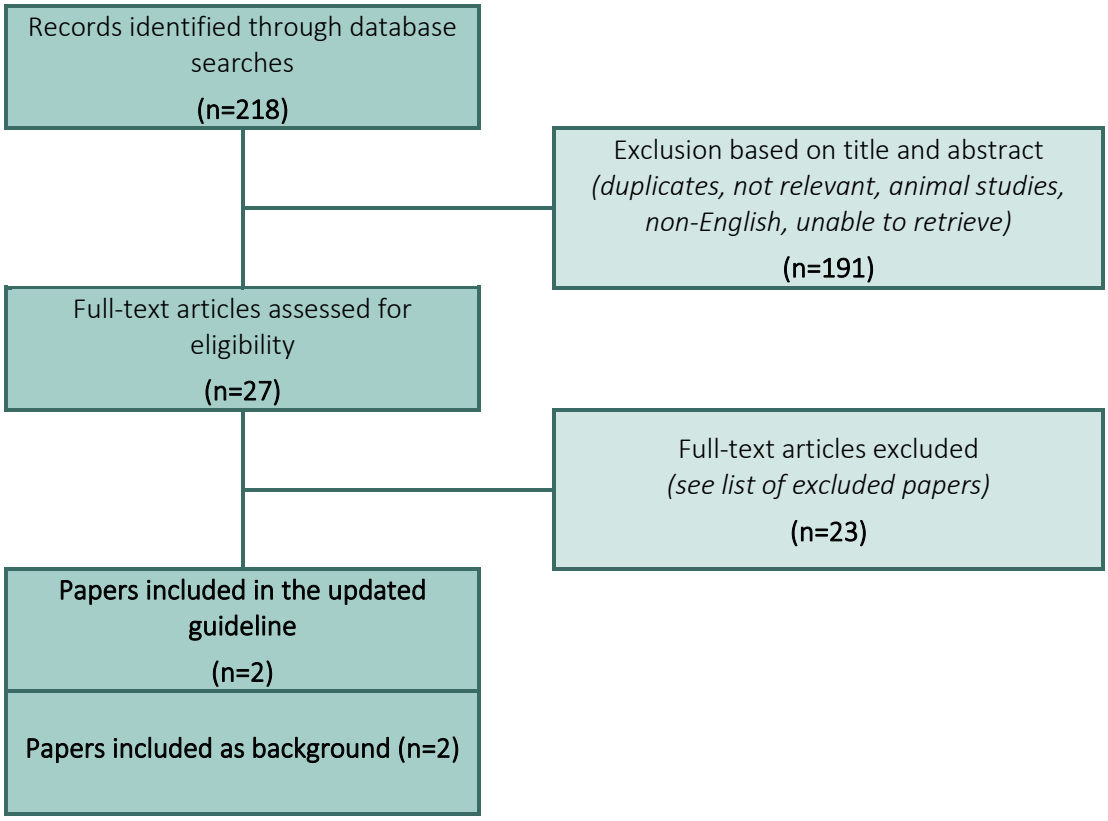


List of excluded papers

	EXCLUSION CRITERIA
Liu, et al., Higher chromosomal abnormality rate in blastocysts from young patients with idiopathic recurrent pregnancy loss. Fertil Steril, 2020. 113(4): p. 853-864.	Small sample size
Lee, et al., Performance of preimplantation genetic testing for aneuploidy in IVF cycles for patients with advanced maternal age, repeat implantation failure, and idiopathic recurrent miscarriage. Taiwan J Obstet Gynecol, 2019. 58(2): p. 239-243.	Small sample size
Iews, et al., Does preimplantation genetic diagnosis improve reproductive outcome in couples with recurrent pregnancy loss owing to structural chromosomal rearrangement? A systematic review. Reprod Biomed Online, 2018. 36(6): p. 677-685.	Heterogeneous results
Sak, et al., Cytogenetic screening in couples with Habitual Abortions. J Gynecol Obstet Hum Reprod, 2019. 48(3): p. 155-158.	This study does not provide materially different data as in the 2017 guideline

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

Flowchart



List of excluded papers

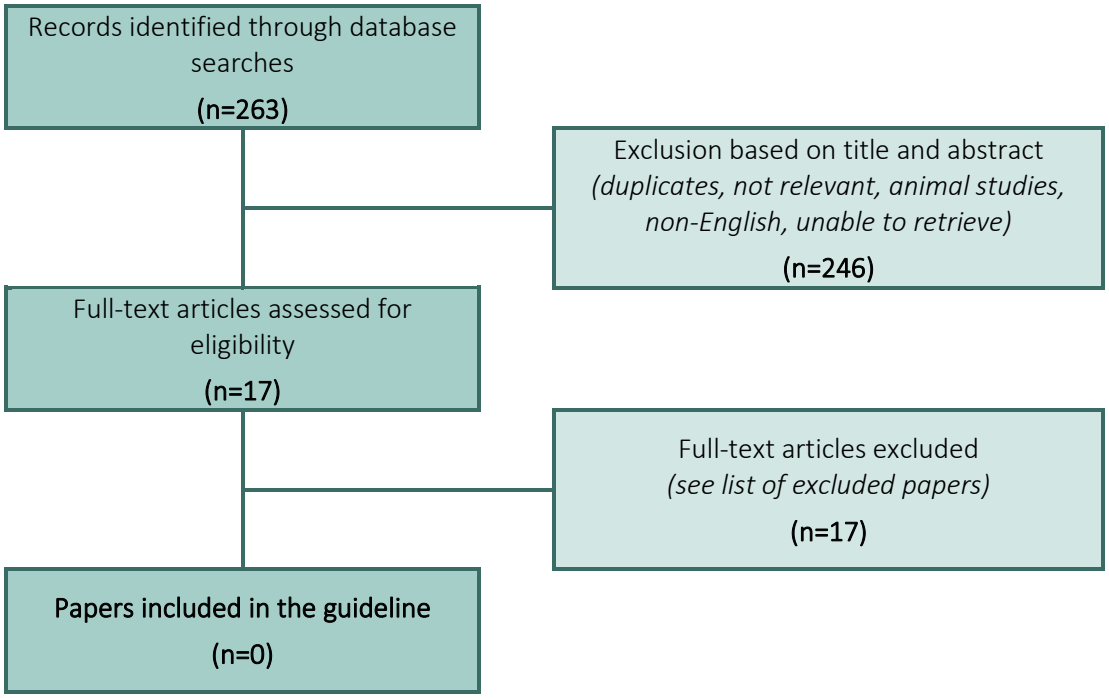
	EXCLUSION CRITERIA
Yang, et al., Prevention of recurrent miscarriage in women with antiphospholipid syndrome: A systematic review and network meta-analysis. Lupus, 2021. 30(1): p. 70-79.	This network meta-analyiss does not provide materially different data as in the 2017 guideline
Lu, et al., Aspirin or heparin or both in the treatment of recurrent spontaneous abortion in women with antiphospholipid antibody syndrome: a meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med, 2019. 32(8): p. 1299-1311.	evidence is very heterogeneous
Karadağ, et al., Aspirin, low molecular weight heparin, or both in preventing pregnancy complications in women with recurrent pregnancy loss and factor V Leiden mutation. J Matern Fetal Neonatal Med, 2020. 33(11): p. 1934-1939.	No control group
Jacobson, et al., Safety and Efficacy of Enoxaparin in Pregnancy: A Systematic Review and Meta-Analysis. Adv Ther, 2020. 37(1): p. 27-40.	Not relevant for the guideline update
Lin, et al., Enoxaparin (or plus aspirin) for the prevention of recurrent miscarriage: A meta-analysis of randomized controlled studies. Eur J Obstet Gynecol Reprod Biol, 2019. 234: p. 53-57.	This meta-analyiss does not provide materially different data as in the 2017 guideline

Chaemsaithong, et al., Does low-dose aspirin initiated before 11 weeks' gestation reduce the rate of preeclampsia? Am J Obstet Gynecol, 2020. 222(5): p. 437-450.	Not RPL
Trasca, et al., Therapeutic Implications of Inherited Thrombophilia in Pregnancy. Am J Ther, 2019. 26(3): p. e364-e374.	Not RPL
Lv, et al., A comparison of effectiveness among frequent treatments of recurrent spontaneous abortion: A Bayesian network meta-analysis. Am J Reprod Immunol, 2018. 80(1): p. e12856.	This network met-analysis does not provide materially different data as in the 2017 guideline
Aslan, et al., Thrombophilia associated gene polymorphisms: Does use of medication, including anti-coagulants, minerals or folic acid, prevent the miscarriages? J Reprod Immunol, 2020. 141: p. 103172.	Small sample size
Wang, et al., Heparin and aspirin combination therapy restores T-cell phenotype in pregnant patients with antiphospholipid syndrome-related recurrent pregnancy loss. Clin Immunol, 2019. 208: p. 108259.	Small sample size
Serapinas, et al., The importance of folate, vitamins B6 and B12 for the lowering of homocysteine concentrations for patients with recurrent pregnancy loss and MTHFR mutations. Reprod Toxicol, 2017. 72: p. 159-163.	Small sample size
Karadağ, et al., Obstetric outcomes of recurrent pregnancy loss patients diagnosed wıth inherited thrombophilia. Ir J Med Sci, 2017. 186(3): p. 707-713.	Small sample size
Yoshihara, et al., Danaparoid is effective and safe for patients with obstetric antiphospholipid syndrome. Mod Rheumatol, 2020. 30(2): p. 332-337.	Small sample size
Ali, et al., Evaluation of etiology and pregnancy outcome in recurrent miscarriage patients. Saudi J Biol Sci, 2020. 27(10): p. 2809-2817.	The intervention is not relevant for the update of the guideline
Nahas, et al., The Prevalence of Thrombophilia in Women With Recurrent Fetal Loss and Outcome of Anticoagulation Therapy for the Prevention of Miscarriages. Clin Appl Thromb Hemost, 2018. 24(1): p. 122-128.	No control group
Ye, et al., Efficacy of Different Treatment Regimens for Antiphospholipid Syndrome-related Recurrent Spontaneous Abortion. Chin Med J (Engl), 2017. 130(12): p. 1395-1399.	This non-randomized study does not provide materially different data as in the 2017 guideline
Rottenstreich, et al., Outcomes of threatened abortions after anticoagulation treatment to prevent recurrent pregnancy loss. Reprod Biomed Online, 2017. 35(4): p. 461-467.	Small sample size
Merviel, et al., Comparison of two preventive treatments for patients with recurrent miscarriages carrying a C677T methylenetetrahydrofolate reductase mutation: 5-year experience. J Int Med Res, 2017. 45(6): p. 1720-1730.	Specific gene polymorphism
Liu, et al., Comparison of therapeutic interventions for recurrent pregnancy loss in association with antiphospholipid syndrome: A systematic review and network meta-analysis. Am J Reprod Immunol, 2020. 83(4): p. e13219.	This meta-analyiss does not provide materially different data as in the 2017 guideline
Han, et al., Inherited thrombophilia and anticoagulant therapy for women with reproductive failure. Am J Reprod Immunol, 2020. p. e13378.	Narrative review
Leaf and Connors, The Role of Anticoagulants in the Prevention of Pregnancy Complications. Clin Appl Thromb Hemost, 2017. 23(2): p. 116-123.	Narrative review
Abou-Saif, et al., The Effect of Low Molecular Weight Heparin in Recurrent Pregnancy Loss: Changes in Radial Uterine Artery Blood Flow and Peripheral Blood NK Cell Fraction. Egypt J Immunol, 2018. 25(2): p. 75-85.	Small sample size

Bao, et al., D-Dimer Assay May Guide LMWH Treatment in Repeated Biochemical Pregnancy Losses in Women with Positive Antiphospholipid Antibody. Clin Lab, 2020. 66(3): p.	This study is not relevant for the update of the guidleine

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

Flowchart



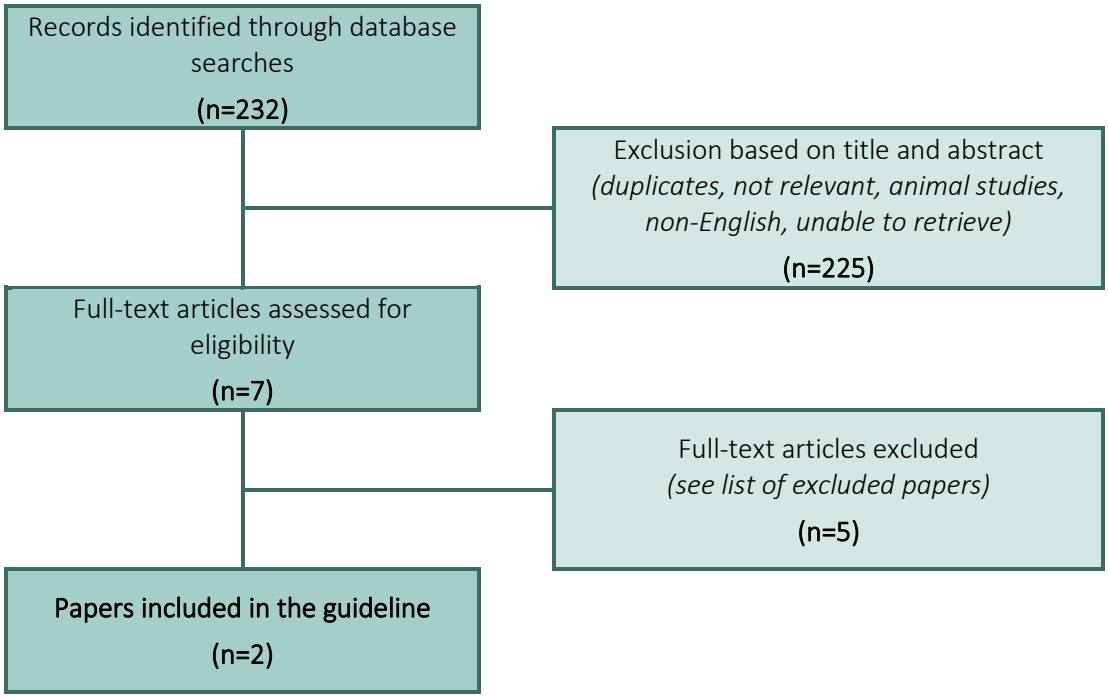
List of excluded papers

	EXCLUSION CRITERIA
Woon, et al., Immunotherapy to improve pregnancy outcome in women with abnormal natural killer cell levels/activity and recurrent miscarriage or implantation failure: A systematic review and meta-analysis. J Reprod Immunol, 2020. 142: p. 103189.	Results regarding IvIg on RPL with increased NK cell numbers are based on 3 non-randomized studies with overlapping patients and serious risk of all kinds of bias
Fu, et al., A randomized controlled trial of etanercept in the treatment of refractory recurrent spontaneous abortion with innate immune disorders. Taiwan J Obstet Gynecol, 2019. 58(5): p. 621-625.	the patients in both groups were treated with heparin, prednisolone, aspirin and cyclosporine, which may really confound the results. In addition, the RCT was not registered in any online trial register, which should be mandatory
Azizi, et al., Cyclosporine A improves pregnancy outcomes in women with recurrent pregnancy loss and elevated Th1/Th2 ratio. J Cell Physiol, 2019. 234(10): p. 19039-19047.	No randomization between cyclosporine vs no cyclosporine. Clinical resulst not valid
Kuon, et al., Pre-Pregnancy Levels of Peripheral Natural Killer Cells as Markers for Immunomodulatory Treatment in Patients with Recurrent Miscarriage. Arch Immunol Ther Exp (Warsz), 2017. 65(4): p. 339-346.	Not relevant for the update of the guideline
Cooper, et al., The effect of prednisolone on endometrial uterine NK cell concentrations and pregnancy outcome in women with reproductive failure. A retrospective cohort study. J Reprod Immunol, 2019. 131: p. 1-6.	Only 28 RPL patients included. No data on pregnancy outcome in patients who received or did not receive prednisolone. No randomization
Martini, et al., Evaluating the Utility of Intralipid Infusion to Improve Live Birth Rates in Patients with Recurrent Pregnancy Loss or Recurrent Implantation Failure. J Hum Reprod Sci, 2018. 11(3): p. 261-268.	Small control group
Canella, et al., Lipid emulsion therapy in women with recurrent pregnancy loss and repeated implantation failure: The role of abnormal natural killer cell activity. J Cell Mol Med, 2021. 25(5): p. 2290-2296.	Narrative review
Coulam, Intralipid treatment for women with reproductive failures. Am J Reprod Immunol, 2020. p. e13290.	Poor quality review with no documentation for the efficacy of intralipid in the prevention of pregnancy loss after RPL
Sun, et al., Association of prednisone and antinuclear antibodies with pregnancy outcomes in women with unexplained recurrent pregnancy loss. Int J Gynaecol Obstet, 2020. p.	
Achilli, et al., The role of immunotherapy in in vitro fertilization and recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril, 2018. 110(6): p. 1089-1100.	Flawed meta-analysis with inclusion of less than half of all randomized RPL patients
Yang, et al., A three-arm, multicenter, open-label randomized controlled trial of hydroxychloroquine and low-dose prednisone to treat recurrent pregnancy loss in women with undifferentiated connective tissue diseases: protocol for the Immunosuppressant regimens for LIving FEtuses (ILIFE) trial. Trials, 2020. 21(1): p. 771.	Study protocol
Yan, et al., Insulin resistance in patients with recurrent pregnancy loss is associated with lymphocyte population aberration. Syst Biol Reprod Med, 2017. 63(6): p. 397-404.	RPL patients with insulin resistance
Alecsandru, et al., Pancreatic autoimmunity: An unknown etiology on patients with assisted reproductive techniques (ART)-recurrent reproductive failure. PLoS One, 2018. 13(10): p. e0203446.	RPl women as subpopulation
Ye, et al., Efficacy of Different Treatment Regimens for Antiphospholipid Syndrome-related Recurrent Spontaneous Abortion. Chin Med J (Engl), 2017. 130(12): p. 1395-1399.	This non-randomized study does not provide materially different data as in the 2017 guideline

Vomstein, et al., Immunological Risk Factors in Recurrent Pregnancy Loss: Guidelines Versus Current State of the Art. J Clin Med, 2021. 10(4): p.	Narrative review
Song, et al., Antiphospholipid Antibody Titers and Clinical Outcomes in Patients with Recurrent Miscarriage and Antiphospholipid Antibody Syndrome: A Prospective Study. Chin Med J (Engl), 2017. 130(3): p. 267-272.	Non-randomized study with small sample size
Mekinian, et al., Refractory obstetrical antiphospholipid syndrome: Features, treatment and outcome in a European multicenter retrospective study. Autoimmun Rev, 2017. 16(7): p. 730-734.	Not RPL

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

Flowchart

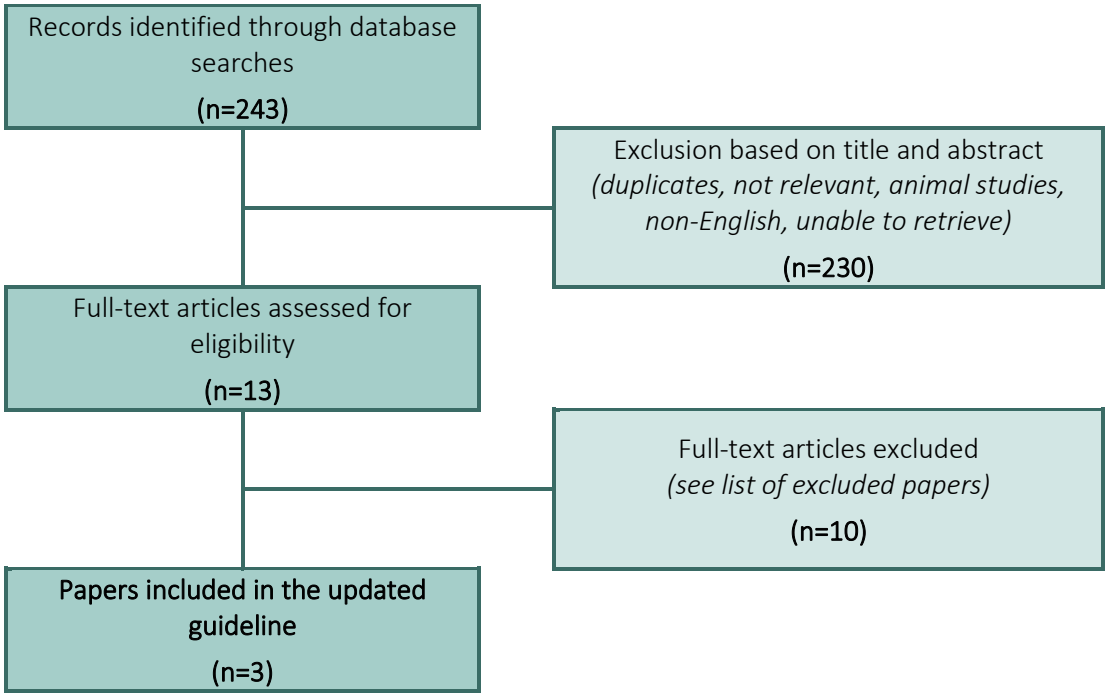


List of excluded papers

	EXCLUSION CRITERIA
Dong, et al., Subclinical hypothyroidism and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril, 2020. 113(3): p. 587-600.e1.	This meta-analysis does not provide materially different data as in the 2017 guideline
Yoshihara, et al., Levothyroxine and subclinical hypothyroidism in patients with recurrent pregnancy loss. Am J Reprod Immunol, 2020. p. e13341.	Not randomized. Large RCTs were included in the updated version of the guideline
Leduc-Robert, et al., Prevalence of thyroid autoimmunity and effect of levothyroxine treatment in a cohort of 1064 patients with recurrent pregnancy loss. Reprod Biomed Online, 2020. 40(4): p. 582-592.	Not randomized. Large RCTs were included in the updated version of the guideline
Xie, et al., Effect of antithyroid antibodies on women with recurrent miscarriage: A meta-analysis. Am J Reprod Immunol, 2020. 83(6): p. e13238.	This meta-analysis does not provide materially different data as in the 2017 guideline
Yan, et al., Insulin resistance in patients with recurrent pregnancy loss is associated with lymphocyte population aberration. Syst Biol Reprod Med, 2017. 63(6): p. 397-404.	Not relevant for the update of this guideline

15. WHICH THERAPEUTIC INTERVENTIONS SHOULD BE OFFERED TO PATIENTS WITH RM DUE TO UTERINE ABNORMALITIES TO INCREASE LIVE BIRTH RATE? (12)

Flowchart



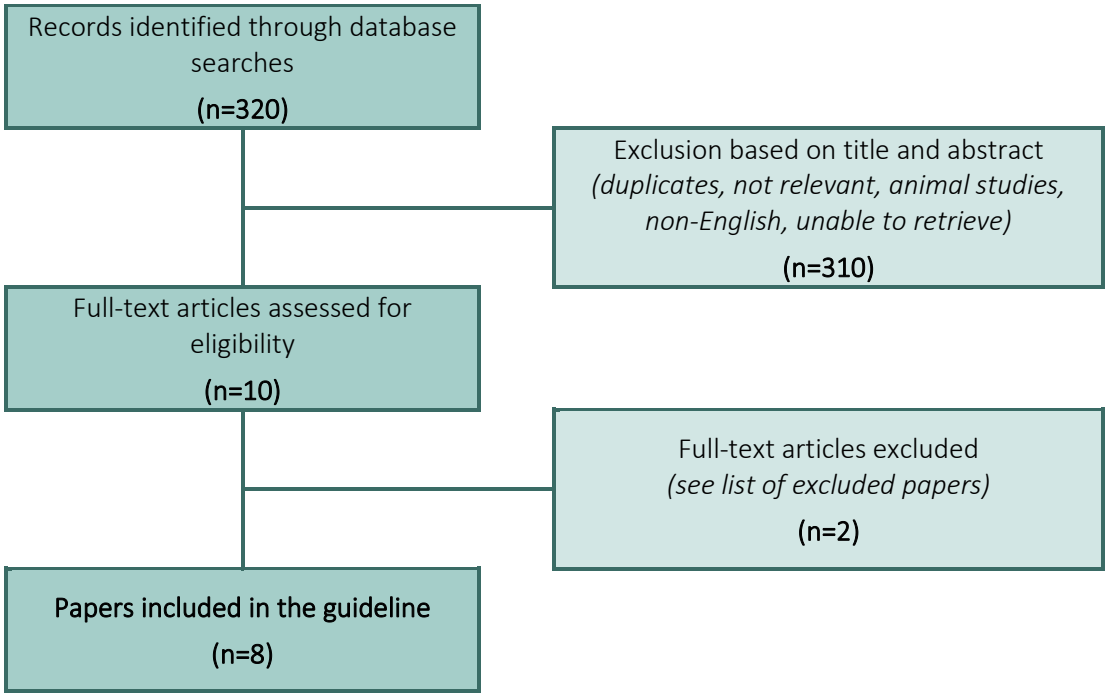
List of excluded papers

	EXCLUSION CRITERIA
Garzon, et al., Hysteroscopic Metroplasty for T-Shaped Uterus: A Systematic Review and Meta-analysis of Reproductive Outcomes. Obstet Gynecol Surv, 2020. 75(7): p. 431-444.	This meta-analysis does not provide materially different data as in the 2017 guideline
Sánchez-Santiuste, et al., Dysmorphic Uteri: Obstetric Results after Hysteroscopic Office Metroplasty in Infertile and Recurrent Pregnancy Loss Patients. A Prospective Observational Study. J Clin Med, 2020. 9(9): p.	Small sample size
Alonso Pacheco, et al., Hysteroscopic outpatient metroplasty for T-shaped uterus in women with reproductive failure: Results from a large prospective cohort study. Eur J Obstet Gynecol Reprod Biol, 2019. 243: p. 173-178.	RPL women as subpopulation
Esteban Manchado, et al., Office hysteroscopic metroplasty with diode laser for septate uterus: a multicenter cohort study. Minim Invasive Ther Allied Technol, 2020. p. 1-7.	RPL women as subpopulation
Di Spiezio Sardo, et al., Long-Term Reproductive Outcomes after Hysteroscopic Treatment of Dysmorphic Uteri in Women with Reproductive Failure: An European Multicenter Study. J Minim Invasive Gynecol, 2020. 27(3): p. 755-762.	Lack of control group
Boza, et al., Surgical correction of T-shaped uteri in women with reproductive failure: Long term anatomical and reproductive outcomes. J Gynecol Obstet Hum Reprod, 2019. 48(1): p. 39-44.	No control group, small number of patients

Whelan, et al., Pregnancy Outcomes in Women With a History of Recurrent Early Pregnancy Loss and a Septate Uterus, With and Without Hysteroscopic Metroplasty. Obstet Gynecol, 2020. 136(2): p. 417-419.	Small number of patients
Ono, et al., Is hysteroscopic metroplasty using the incision method for septate uterus a risk factor for adverse obstetric outcomes? J Obstet Gynaecol Res, 2019. 45(3): p. 634-639.	Small sample size
Ono, et al., Retrospective cohort study of the risk factors for secondary infertility following hysteroscopic metroplasty of the uterine septum in women with recurrent pregnancy loss. Reprod Med Biol, 2018. 17(1): p. 77-81.	Small number of patients, no control group
Elsokkary, et al., Assessment of hysteroscopic role in management of women with recurrent pregnancy loss. J Matern Fetal Neonatal Med, 2018. 31(11): p. 1494-1504.	Very poor-quality study

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

Flowchart

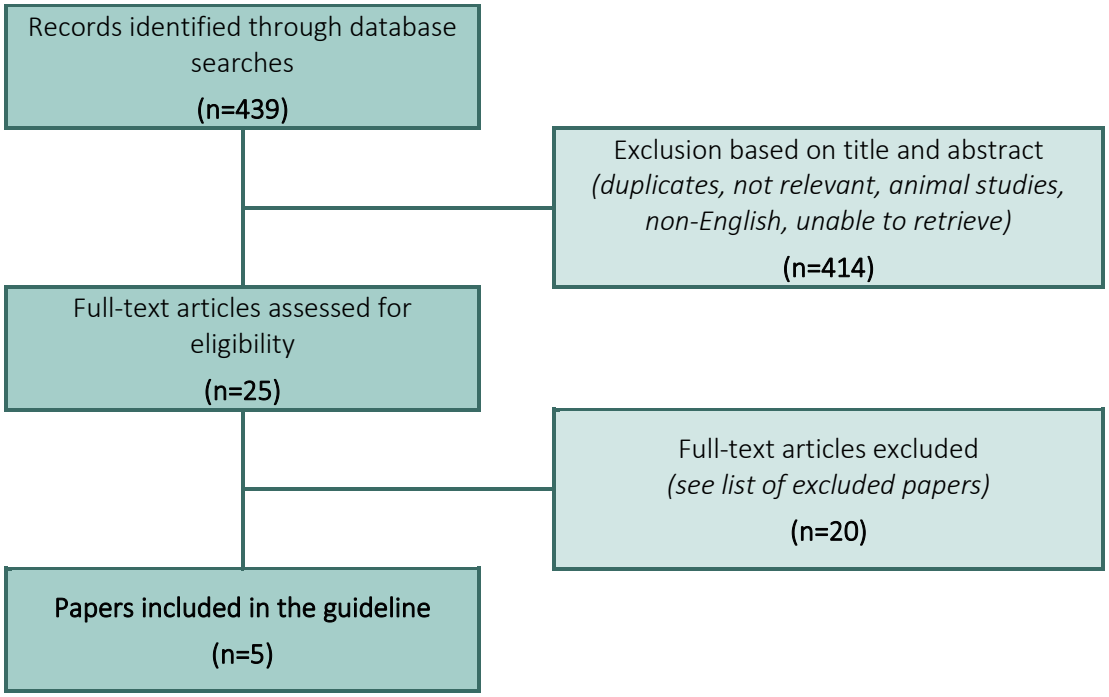


List of excluded papers

	EXCLUSION CRITERIA
Nazari, et al., Comparison between sperm parameters and chromatin in recurrent pregnancy loss couples after antioxidant therapy. J Family Med Prim Care, 2020. 9(2): p. 597-601.	Nonrandomized trial with Small sample size
Hamidian, et al., The effect of vitamin C on the gene expression profile of sperm protamines in the male partners of couples with recurrent pregnancy loss: A randomized clinical trial. Clin Exp Reprod Med, 2020. 47(1): p. 68-76.	Small sample size, allocation bias

17. WHICH THERAPEUTIC INTERVENTIONS SHOULD BE OFFERED TO PATIENTS WITH UNEXPLAINED RM TO INCREASE LIVE BIRTH RATE? (16)

Flowchart



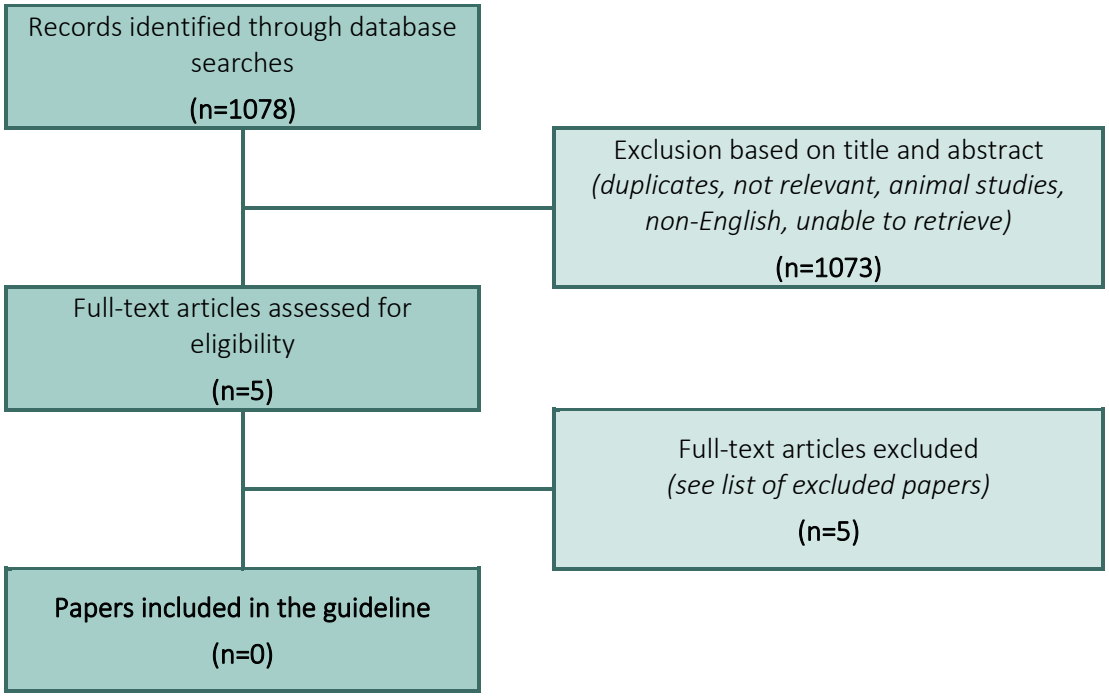
List of excluded papers

	EXCLUSION CRITERIA
Yang, et al., A three-arm, multicenter, open-label randomized controlled trial of hydroxychloroquine and low-dose prednisone to treat recurrent pregnancy loss in women with undifferentiated connective tissue diseases: protocol for the Immunosuppressant regimens for LIving FEtuses (ILIFE) trial. Trials, 2020. 21(1): p. 771.	Study protocol
Achilli, et al., The role of immunotherapy in in vitro fertilization and recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril, 2018. 110(6): p. 1089-1100.	Flawed meta-analysis
Christiansen, et al., Treatment with intravenous immunoglobulin in patients with recurrent pregnancy loss: An update. J Reprod Immunol, 2019. 133: p. 37-42.	Not relevant for the update of the guideline
Plaçais, et al., Intralipid therapy for unexplained recurrent miscarriage and implantation failure: Case-series and literature review. Eur J Obstet Gynecol Reprod Biol, 2020. 252: p. 100-104.	Small study with only 10 RPL patinets
Chen, et al., Effect of immunotherapy on patients with unexplained recurrent spontaneous abortion. Ann Palliat Med, 2020. 9(5): p. 2545-2550.	
Hou, et al., The optimal timing of immunotherapy may improve pregnancy outcome in women with unexplained recurrent pregnancy loss: A perspective follow-up study in northeastern China. Am J Reprod Immunol, 2020. 83(4): p. e13225.	Only 13% of patients are classified as unexplained. No control group
Carp, Immunotherapy for recurrent pregnancy loss. Best Pract Res Clin Obstet Gynaecol, 2019. 60: p. 77-86.	Narrative review
Coccia, et al., The effect of low-dose ovarian stimulation with HMG plus progesterone on pregnancy outcome in women with history of recurrent pregnancy loss and secondary infertility: a retrospective cohort study. Gynecol Endocrinol, 2018. 34(6): p. 528-531.	Heterogeneous population
Zafardoust, et al., Efficacy of Intrauterine Injection of Granulocyte Colony Stimulating Factor (G-CSF) on Treatment of Unexplained Recurrent Miscarriage: A Pilot RCT Study. J Reprod Infertil, 2017. 18(4): p. 379-385.	A pilot RCT
Blomqvist, et al., Acetylsalicylic acid does not prevent first-trimester unexplained recurrent pregnancy loss: A randomized controlled trial. Acta Obstet Gynecol Scand, 2018. 97(11): p. 1365-1372.	Treatment was only started when fetal heart action was confirmed in week 6-7
Xu, et al., Clinical Efficacy of Low Molecular Heparin on Unexplained Recurrent Spontaneous Abortion. Clin Lab, 2018. 64(6): p. 1037-1040.	No randomization
Jiang, et al., The role of low molecular weight heparin on recurrent pregnancy loss: A systematic review and meta-analysis. Taiwan J Obstet Gynecol, 2021. 60(1): p. 1-8.	Meta-analysis based on papers that cannot be trusted (under investigation)
Awolumate, et al., Role of Low Molecular Weight Heparin in the Management of Unexplained Recurrent Pregnancy Loss: A Review of Literature. Cureus, 2020. 12(10): p. e10956.	Narrative review
Cetin, et al., The impact of low molecular weight heparin on obstetric outcomes among unexplained recurrent miscarriages complicated with methylenetetrahydrofolate reductase gene polymorphism. Ginekol Pol, 2017. 88(5): p. 260-265.	Small sample size and heterogenous study population
Sun, et al., Association of prednisone and antinuclear antibodies with pregnancy outcomes in women with unexplained recurrent pregnancy loss. Int J Gynaecol Obstet, 2020. p.	Non-randomized study with relatively small sample size of heterogeneous patients
Jafarzadeh, et al., Intravenous immunoglobulin G treatment increases live birth rate in women with recurrent miscarriage and modulates regulatory and exhausted regulatory T cells frequency and function. J Cell Biochem, 2019. 120(4): p. 5424-5434.	Non-randomized study with a small sample size of 44 RPL patients

Ou and Yu, Efficacy of aspirin, prednisone, and multivitamin triple therapy in treating unexplained recurrent spontaneous abortion: A cohort study. Int J Gynaecol Obstet, 2020. 148(1): p. 21-26.	Nonrandomized study
Dobson and Jayaprakasan, Aetiology of recurrent miscarriage and the role of adjuvant treatment in its management: a retrospective cohort review. J Obstet Gynaecol, 2018. 38(7): p. 967-974.	retrospective study with no randomization and very small treatment groups
Ling, et al., Low dose Cyclosporin A treatment increases live birth rate of unexplained recurrent abortion - initial cohort study. Clin Exp Obstet Gynecol, 2017. 44(2): p. 230-235.	
Fox, et al., Luteal phase HCG support for unexplained recurrent pregnancy loss - a low hanging fruit? Reprod Biomed Online, 2017. 34(3): p. 319-324.	not randomized study with each patient treated in several monitored cycles

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

Flowchart



List of excluded papers

	EXCLUSION CRITERIA
Iews, et al., Does preimplantation genetic diagnosis improve reproductive outcome in couples with recurrent pregnancy loss owing to structural chromosomal rearrangement? A systematic review. Reprod Biomed Online, 2018. 36(6): p. 677-685.	Not relevant for this question.
Pourakbari, et al., Cell therapy in female infertility-related diseases: Emphasis on recurrent miscarriage and repeated implantation failure. Life Sci, 2020. 258: p. 118181.	Narrative review
Nonaka, et al., Treatment for patients with recurrent fetal losses positive for anti-cardiolipin beta2 glycoprotein I antibody using Sairei-to (Chai-ling-tang) and low-dose aspirin. J Obstet Gynaecol Res, 2019. 45(3): p. 549-555.	Small sample size
Lee, et al., Performance of preimplantation genetic testing for aneuploidy in IVF cycles for patients with advanced maternal age, repeat implantation failure, and idiopathic recurrent miscarriage. Taiwan J Obstet Gynecol, 2019. 58(2): p. 239-243.	Not relevant for this question
Maithripala, et al., Prevalence and Treatment Choices for Couples with Recurrent Pregnancy Loss Due to Structural Chromosomal Anomalies. J Obstet Gynaecol Can, 2018. 40(6): p. 655-662.	Not relevant for this question