ESHRE Guideline:

Recurrent Pregnancy Loss

Stakeholder Review report

The ESHRE Guideline "Recurrent Pregnancy Loss" was open for stakeholder review between 30 June and 15 August 2017. The draft of the document was published on the ESHRE website. Stakeholders were invited to submit comments through mailings, and advertisements during the ESHRE annual meeting in Geneva, and on social media. For patient input, the draft guideline and draft patient version were send to European patient organization (through Fertility Europe); and miscarriage organizations (Ireland, UK).

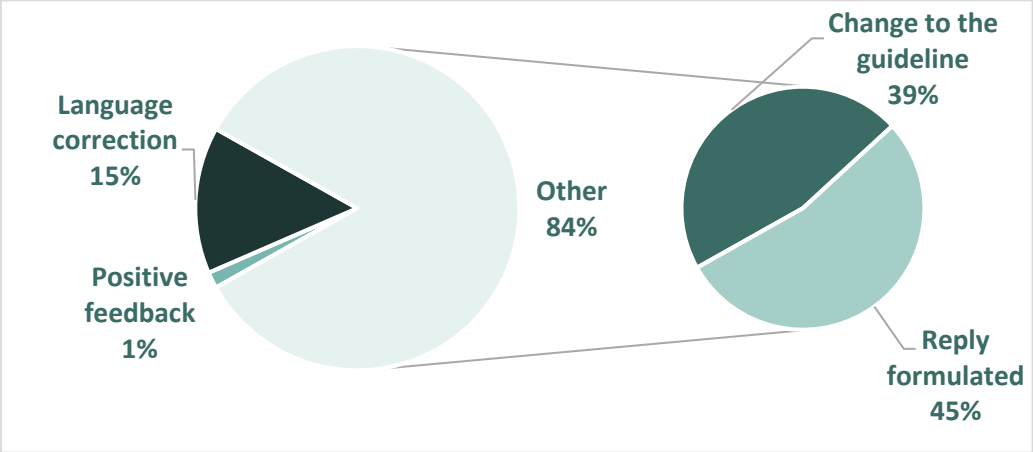
Results

Twenty-three reviewers, representing 15 countries, 2 national societies (Royal College of Obstetricians and Gynaecologists, and SIGO - AOGOI – AGUI) and 1 international research group (ESHRE/ESGE CONUTA Group), submitted a total of 307 comments (on average 13 comments per reviewer). All reviewers are listed on page 2 and in annex 6 of the guideline document.

All comments were assessed by the research specialist and the guideline group members, and, if relevant, changes were made to the guideline (see also Figure 1):

- 5 comments (1,6 %) provided positive feedback that did not require any action from the working group,
- 45 comments (14,7 %) requested improvements of language and format of the guideline, and these were all modified in the guideline,
- 257 comments (83,7 %) were comments to the content, requesting corrections, modifications, or addition of further information. Of these, 119 comments were judged relevant and corresponding changes were made to the paper. The working group formulated a reply to the remaining 138 comments, detailing why the comment was not incorporated in the paper.

Figure 1: results of the stakeholder review: actions for the comments received.



List of reviewers

Representative	Organization
RCOG Guidelines Committee Bethany King	Royal College of Obstetricians and Gynaecologists
ESHRE/ESGE CONUTA Group Grigoris Grimbizis	ESHRE/ESGE CONUTA Group
Giovanni Scambia SIGO President Elsa Viora AOGOI President Nicola Colacurci AGUI President	SIGO - AOGOI – AGUI (Italy)

Reviewer	Country
Stephan Gordts	Belgium
T C Li	China
Fang Ma	China
Henriette Svarre Nielsen	Denmark
Aboubakr Elnashar	Egypt
Thomas Strowitzki	Germany
Christiane Kling	Germany
Pratip Chakraborty	India
Mayumi Sugiura-Ogasawara	Japan
Raminta Bausyte	Lithuania
Michal Kunicki	Poland
Kersti Lundin	Sweden
Recurrent Pregnancy Loss group LUMC Harjo Verburg, Sandra Dieben, Lisa Lashley, Marie-Louise van der Hoorn	The Netherlands
H.D.L. Ockhuijsen	The Netherlands
Ahmet Berkiz Turp	Turkey
Alessandra Pipan	UAE
Hena Zaheer	UAE
Mahmoud Moussa	UK
Shehnaaz Jivraj	UK
Arianna D'Angelo	UK
Ying Cheong	UK
Joe Leigh Simpson	USA
Channing Burks, Mary D. Stephenson, Theresa S. Falcon-Cullinan	USA

List of comments

Chapter	Reviewer	Page	Line	Comment	Reply GDG
4	hena zaheer	PGD		I am working in the largest public sector in the UAE and are into doing PGS /PGD from 2007 which has approximately 800 cycles per year and have 33% of our patients undergoing PGD/PGS 15% of our patients undergoing PGS are due to recurrent pregnancy loss, all had a day 3 biopsy an the ongoing pregnancy rate is 33% which is not statistically different for the general IVF/ICSI patients This statistics are from an ongoing study in our center regarding the PGD/ PGS outcome We are almost coming to a conclusion that day3 biopsy is not of help in women with recurrent pregnancy loss in terms of ongoing pregnancy rate	We are looking forward to reading your paper on this important topic, and are happy to see that the conclusion (not recommending PGD in RPL) is similar to what we recommend in the guideline.
6	T C Li	6.2 3		It is a very substantial piece of work, many congratulations to the team. The only comment I have relates to 6.23 regarding NK cell. I think it would be better all round to modify it to say "There is insufficient evidence to recommend routine NK cell testing in women with RPL"	We have changed the recommendation as suggested
2	H.D.L. Ockhuijse n	32	765-766	Recommendations: no alcohol during the pregnancy and limit alcohol consumption in the preconception phase? What is excessive alcohol consumption, how many alcohol consumptions is recommended	We agree that there is no definition of excessive or limited alcohol consumption. However, also for women without RPL, such definition does not exist. Therefore, we have stated that couples should limit alcohol intake.
1	H.D.L. Ockhuijse n	25	525	decrease in the chance of live birth with increasing female age (Lund et al., 2012).= a significant decrease?	We added that the increase was significant
1	H.D.L. Ockhuijse n	25	517-519	The sentences need more explanation. Habbema et al states: Without IVF, couples should start no later than age 32 years for a one-child family, at 27 years for a two child family, and at 23 years for three children.	We added a sentence with the data to achieve a one-child family.
1	H.D.L. Ockhuijse n	25	501	Patients should be reassured that there is no evidence that stress causes pregnancy loss. No evidence or insufficient/no strong evidence?	To address this and other comments, we have rephrased this recommendation: Stress is associated with RPL, but patients should be informed that there is no evidence that stress is a direct cause of pregnancy loss.

0	H.D.L. Ockhuijsen	23, 26,	448, 462	Two examples: a series of papers and two small studies evaluating…. The guideline is not consistent in the naming of the designs of the different studies. For the reader it is clearer when the design of the study is mentioned.	We have added the study type throughout the guideline
1	Fang Ma	P28	L616	The aboved suggestion for this section.	We have changed the order of the topics according to importance/significance.
1	Fang Ma	P24	L461	For the "Risk factors" section, life style were involved, I'm feeling the logical arrangement is out of order, maybe according to the Bio-psycho-social Medical Mode?	We have changed the order of the topics according to importance/significance.
A	Fang Ma	P15	L156-157	For the definition of RPL, it's not very clear, I think should be more accurate and brief in one sentence (just mention natural fertility, IVF not included?) after the one definition sentence, further description are continued.	We added a sentence clarifying that both Pregnancy losses after spontaneous conception and after ART are included in the definition
0	Fang Ma	P7	10	For the investigation and treatment of RPL, the contents are a kind of too scattered. For example, about the investigation section, it might be edited as the different summarized factors ,then listed the specific contents, like genetic factors, ovarian function, immune disorder…. About Treatment, the same suggestion, also, it might be summarized the unrecommended or recommended, and added the subject classification; shown logically and clearly.	We will work on a flyer presenting the information of recommended test and treatments as suggested.
0	Fang Ma	P6	L152	The evidence of strength, may we have the description of the grade, and ABCD are more widely used?	It was decided to use the widely accepted GRADE approach for grading recommendations. Hence, this cannot be changed.
7	Pratip Chakraborty	73	2137	From my research findings I strongly feel that measurement of serum homocysteine levels should be recommended in RPL affected PCOS women especially the patients suffering from Unexplained spontaneous miscarriage. The incidence rate of hyperhomocysteinemia is increasing in alarming fashion in South-Asian countries including India cueing to an epigenetic effect of the same On RPL. A high insulin level which is frequently seen in sub-continental women in particular may add up to this effect of increase in homocysteine through defective Transsulfuration.	We added text and references to the justification section. 'Furthermore, we realize that there is a geographical and ethnic variation in the genetic pathways of the homocysteine metabolism (Wilcken et al. J Med Genet 2003, Binia et al. Genes NUtr 2014).'
14	Mayumi Sugiura-Ogasawara	106	3275	Bromocriptine treatment is recommended based on only one prospective study including a small number (strong). I feel that further study is necessary to recommend "strongly".	We corrected this to a weak recommendation as indeed the evidence is limited and there are no further arguments to justify a strong recommendation

<table>
<tr>
<td>12</td>
<td>Mayumi Sugiura-Ogasawara</td>
<td>96</td>
<td>2983</td>
<td>ESHRE guideline suggests antepartum administration with aspirin and UFH in patients with APS who fulfil the International criteria (conditional). ESHRE guideline described that it should be noted there is significant risk of bias in the included studies.
I believe that details of significant risk of bias should be described because APS is the only treatable etiology.
Methods of diagnosis and titers of aCL or LA were different in each study as follows (Table). The international criteria on APS revised in 2006 recommends that at least two kinds of reagents (aPTT and RVVT) should be tested. Recently, LA, but not aCL, was reported to be predictive for adverse pregnancy outcomes in obstetric APS (1, 2).

<table>
<tr><th></th><th>aCL</th><th>LA</th><th>Case (n)</th><th>Control (n)</th><th>Live</th></tr>
<tr><td>Cowchock S 1992</td><td>IgG>30 IgM>11</td><td>dRVVT or aPTT</td><td>A+scUFH (26)</td><td>A+PSL (19)</td><td>73.1</td></tr>
<tr><td>Silver RK 1993</td><td>IgG>8 IgM>5</td><td>dRVVT</td><td>A (22)</td><td>A+PSL (12)</td><td>100</td></tr>
<tr><td>Kutteh WH 1996</td><td>IgG>=27 IgM>=27</td><td>No</td><td>A+scUFH (25)</td><td>A (25)</td><td>80.0</td></tr>
<tr><td>Rai R 1997</td><td>IgG>5 IgM>3</td><td>RVVT aPTT (exclude SLE)</td><td>A+scUFH (45)</td><td>A (45)</td><td>71.1</td></tr>
<tr><td>Pattison 2000</td><td>IgG>=5 IgM>=5</td><td>aPTT, dRVVT, KCT</td><td></td><td>A (20)</td><td></td></tr>
<tr><td>Farquharson 2002</td><td>IgG>9 IgM>5</td><td>dRVVT</td><td>A+scLMWH (51)</td><td>A (47)</td><td>78.4</td></tr>
<tr><td>Franklin and Kutteh 2002</td><td>IgG>20 IgM>20</td><td>dRVVT</td><td>A+LMWH (25)</td><td></td><td>76.0</td></tr>
<tr><td>Noble LS and Kutteh WH 2005</td><td>IgG>20 IgM>20</td><td>dRVVT aPTT</td><td>A+scLMWH (25)</td><td>A+scUFH (25)</td><td>84</td></tr>
<tr><td>Laskin 2009</td><td>IgG>15 IgM>25</td><td>dRVVT, PTT-LA, DilPT,KCT</td><td>A+scLMWH (22)</td><td>A (21)</td><td>77.3</td></tr>
</table>

1. Lockshin MD, Kim M, Laskin CA, Guerra M, Branch DW, Merrill J, Petri M, Porter TF, Sammaritano L, Stephenson MD, Buyon J, Salmon JE.. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. Arthritis Rheum 2012; 64: 2311-8.
2. 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.</td>
<td>We have stated in our recommendation “who fulfill the laboratory criteria of APS”. We are aware of different diagnostics tests, but we feel that it is to be decided by the laboratory which test to use, and to provide the appropriate titers for the test. Detailed assessment of the different tests available is outside the scope of the current guideline.</td>
</tr>
<tr>
<td>6</td>
<td>Mayumi Sugiura-</td>
<td>53</td>
<td>1441</td>
<td>Regarding ANA, we published article as follows,</td>
<td>We included this reference in the section on ANA.</td>
</tr>
</table>

	Ogasawara			In our previous study, 39 of the 225 (17.3%) women with a history of two consecutive first trimester miscarriage had ANA compared with 33 of 740 (4.5%) control women (p<0.001, OR 4.5). 43 of 186 (23.1%) ANA-negative patients and 6 of 39 (15.4%) ANA –positive patients had a further miscarriage. This means that ANA are associated with miscarriage, but ANA- positive patients with no antiphospholipid antibodies do not require medication. The presence of ANA does not predict subsequent pregnancy loss. I believe that this letter should be considered to be included in the ANA section since the results are reliable and important and the study design is prospective though this is not full-text. Ogasawara M, Aoki K, Kajiura S, Yagami Y. Are antinuclear antibodies predictive of recurrent miscarriages? Lancet 1996; 347:1183-1184.	
4	Mayumi Sugiura-Ogasawara	39	974	Ongoing pregnancies with unbalanced translocations was 2.9% in carrier couples with RPL in the Sugiura-Ogasawara's study, 2004. I think this is not very rare.	We have added the results of the study to the text and rephrased the sentence
4	Mayumi Sugiura-Ogasawara	37	934	ESHRE guideline concluded that no clear effect of genetic testing of the pregnancy tissue on prognosis (subsequent live birth) has been described so far. However, our previous study proved that the patients with a previous normal embryonic karyotype miscarried significantly more frequently prospectively (p=0.001, OR 2.6, 95%CI 1.29-5.32)(1). 44 of 71 patients (62.0%) whose embryonic karyotypes were normal miscarried subsequently, as opposed to 23 of 60 patients (38.3%) with abnormal embryonic karyotypes in our previous study (1). I believe that this should be considered to be included in this section. Furthermore, the prevalence of the abnormal embryonic karyotype was 41.1% and that of truly unexplained cause, of patients without conventional causes in whom the embryonic karyotype was normal, was 24.5% in a total of 482patients who underwent both embryonic karyotype determination and conventional examination (2). I believe that the difference between abnormal embryo and abnormal uterine might be important for patients. Patients with RPL caused by the abnormal embryonic karyotype might be targets who wish for preimplantation genetic testing for aneuploidy though RCT has not been conducted.	We state that Genetic analysis of pregnancy tissue is not routinely recommended but it could be performed for explanatory purposes, which is consistent with the suggestion made. The study of Ogasawara 2000 was excluded from the summary of evidence, as the data were included in the review of Van den Berg 2012.

				1. Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in relation to the number of previous miscarriages. Fertil Steril 2000; 73: 300-304. 2. Sugiura-Ogasawara M, Ozaki Y, Katano K, Suzumori N, Kitaori T, Mizutani E. Abnormal embryonic karyotype is the most frequent cause of recurrent miscarriage. Hum Reprod 2012; 27: 2297-2303.	
14	Ying Cheong		3180-3187	2. This point pertains to reference to Mary Stephenson's paper Lines 3180-3187 - small minor point - progesterone administration was at 3 days after LH surge.	We copied this sentence from the abstract of the paper stating "100–200 mg every 12 hours starting 3 days after the LH surge"
1	Ying Cheong		stress	1. The recommend around stress 'patients should be reassured that there is no evidence that stress causes pregnancy loss.' is scientifically completely justified. I do however worry that this may lead to 'dismissal' of patients' stress. As we know, RPL patients are often highly anxious and 'stress' and this is part of a known association and a disease burden of RPL. Perhaps a justification sentence after - highlighting the fact that clinicians should be sensitive to these needs and provide the necessary individualisation supportive and psychological care would be useful? I know this has been discussed in the clinical set up etc in the first part of the review, but a lot of clinicians only read the recommendations without reading the text!	To address this and other comments, we have rephrased this recommendation: Stress is associated with RPL, but patients should be informed that there is no evidence that stress is a direct cause of pregnancy loss.
17	Thomas Strowitzki		Page 127	The following recommendation: "A series of serious adverse effects has been reported after the use of intravenous lipid emulsions: acute kidney injury, cardiac arrest, acute lung injury, venous thromboembolism, fat embolism, fat overload syndrome, pancreatitis, allergic reactions and increased susceptibility to infection (Hayes et al., 2016). " "Recommendation: Intralipid therapy should not be used for improving live birth rate in unexplained RPL, as it could be harmful for the mother. Strong ⊕□□□" The only literature as mentioned is Hayes et al: "Systematic review of clinical adverse events reported after acute intravenous lipid emulsion administration." This is completely different from diluted intralipid use in repeated pregnancy loss. In some of the studies authors describe intralipid use as antidot or treatment in cases of intoxication with lipophilic medical drugs. They state in the abstract: "The dosing regimen for the clinical toxicology indications differs significantly from those used for parenteral nutrition." To summarize they included 27 animal studies and 87 human studies with	We corrected the section and the recommendation, highlighting the differences in doses used between the studies, and the lack of adverse events in RRPL studies. The recommendation was changed to 'There is insufficient evidence to recommend intralipid therapy for improving live birth rate in women with unexplained RPL.'

				dosages which differ dramatically from those used in RPL. They didn't include or identify studies with diluted intralipid treatment in RPL patients. Consequently their conclusion is: „Adverse effects seem to be proportional to the rate of infusion as well as total dose received." Studies in the ESHRE guideline which describe intralipid infusions in RPL have used the following concentrations: Roussev et al., 2008: 2-4 ml Intralipid 20% in 250 ml saline, time of infusion 1h, n=50 Meng et al., 2015: 250 ml Intralipid 20%, time of infusion 2h, no side effects reported, n=96 To my knowledge there is one patient with renal failure and cardiac arrest described in the literature after having received 2580 ml Intralipid in 24 h. Most patients in the review by Hayes et al. represent ICU patients or neonates and this is in sharp contrast to our otherwise healthy young women trying to conceive. Authors give the following limitations:: "The search criteria and citation screening were designed to be as inclusive as possible in order to estimate the clinical adverse effects associated with ILE given in doses typically used to treat acute poisonings, but the studies included in this systematic review were consistently of low or very low quality according to GRADE criteria. Furthermore, included studies could have suffered from reporting bias, in that not all adverse effects reported were related to the use of ILE and those that do occur were not always reported. Neonates and small children seem to be at higher risk of adverse events." So I have some concern if this somehow superficial and irritating statement should be part of guidelines of RPL which will be read by patients as well.	
8	Thomas Strowitzki			My only major concern is the recommendation on 3D ultrasound. You might be more familiar with this issue. However guidelines should take into account what is feasible in centers and I have some doubt that favouring 3D and neglecting endoscopy is really what we should claim in a guideline.	After reviewing the evidence and all comments, we still recommend 3D US as a firstline option. We did change the recommendation on MRI, now stating that MRI is not recommended as first line option, but can be used when 3D US is unavailable. (based on lower accuracy and higher costs compared to 3D US.
4	Kersti Lundin	11.2		"PGS" and "PGD" should be renamed to follow more closely the new International glossary (in which ESHRE was also involved): *Preimplantation*	We have updated the terminology to the new international glossary

				genetic testing (PGT): A test performed to analyze the DNA from oocytes (polar bodies) or embryos (cleavage stage or blastocyst) for HLA-typing or for determining genetic abnormalities. These include: PGT for aneuploidies (PGT-A); PGT for monogenic/single gene defects (PGT-M); and PGT for chromosomal structural rearrangements (PGT-SR). see also article and ref at https://academic.oup.com/humrep/article/doi/10.1093/humrep/dex234/4049537/The-International-Glossary-on-Infertility-and?guestAccessKey=c479cc3c-cd08-4794-8317-b3b2a34e3a32	
4	Kersti Lundin		904-906	It is stated: *Most embryos that miscarry early are morphologically abnormal (Philipp et al., 2003). The use of embryoscopy, direct visualization of the embryo to assess these abnormalities, has shown that they occur in 86-91% of miscarriages where an embryo is present. (-->*To me, as an embryologist, this sounds as if the morphology of the early preimplantation embryo in is discussed, which of course it is not. But perhaps it could be written as: *Most ~~embryos~~ concepti that miscarry early are morphologically abnormal (Philipp et al., 2003). The use of embryoscopy, ie. direct visualization of the embryo or early foetus in utero ~~to assess these abnormalities~~, has shown that ~~they~~ these abnormalities occur in 86-91% of miscarriages where an embryo is present.)*	Corrected as suggested
A	Kersti Lundin		156-158 and 200-203	*It is stated: A pregnancy loss (miscarriage) is defined as the spontaneous demise of a pregnancy before the fetus 157 reaches viability. The term therefore includes all pregnancy losses (PLs) from the time of conception until 24 weeks of gestation.* *A pregnancy in the definition is confirmed at least by either serum or urine b-hCG, i.e. including non-visualized pregnancy losses (biochemical pregnancy losses and/or resolved and treated pregnancies of unknown location).). If identified as such, ectopic and molar pregnancies should not be excluded from the definition. (-->So does this mean that ectopic are included in RPL as stated here, or not included, as stated in lines 135-136? Perhaps clarify?)*	Corrected: If identified as such, ectopic and molar pregnancies should not be included from the definition.
0	Kersti Lundin		134-136	*It is stated: Recurrent Pregnancy Loss (RPL) is defined as the loss of two or more pregnancy losses. It excludes ectopic pregnancy and molar pregnancy. (-->There must be one "loss" to many, I don´t think you can have a loss of losses.)*	Corrected

15	Aboubakr Elnashar	116	3583	If there is a history of second-trimester PLs and suspected cervical weakness, serial cervical sonographic surveillance. The timing of this surveillance is important. It is recommended to be between 16 w and 24 w	Although relevant, we have decided not to add details on the timing of serial cervical sonographic surveillance, as we did not include this in our literature searches.
15	Aboubakr Elnashar	115	3548	The degree of intrauterine adhesion should be considered. Severe adhesions (more than one half of uterine cavity should be treated.	We added a sentence in the justification section stating that for severe adhesions, benefits of surgery may outweigh possible harms.
15	Aboubakr Elnashar	114	3531	Treatment of submucosal fibroid. Recommendation should be there is insufficient evidence to recommend removal.(Not there is no evidence)	We changed the recommendation stating there is insufficient evidence.
14	Aboubakr Elnashar	103	3154	Euthyroid women with thyroid antibodies: insufficient evidence to support treatment with levothyroxine. What is definition of euthyroid, TSH more than 2.5 is not euthyroid.?	We added the reference range used for TSH in the text.
14	Aboubakr Elnashar	102	3151	Treatment of subclinical hypothyroidism may reduce the risk of miscarriage, but the potential benefit of treatment should be balanced against the risks. What are the risks, if any?	We added some text about the risks of subclinical hypothyroidism treatment: 'In addition, levothyroxine therapy during pregnancy might carry the potential risk of adverse child neurodevelopment outcomes, since high maternal free thyroxine concentrations during pregnancy are recently be reported to be associated with lower child IQ and lower grey matter and cortex volume (Korevaar et al. 2016).
4	Aboubakr Elnashar	38	937	The genetic investigations should not be done except after 3 successive pregnancy losses and not 2	We agree that genetic testing should not routinely be performed in allRPL couples, hence we recommend that it can be considered, instead of it should be performed.
4	Aboubakr Elnashar	37	899	The sequence of investigations is important. It should not be started by screening for genetic factors. The sequence should be according to prevalence of the cause. So, to start with anatomical, endocrinological and metabolic, male factor and lastly genetic factors	The order of the chapters was decided by the group. It was decided that the genetic chapter should be listed first, as it has been suggested only to proceed to other tests in case of an euploid pregnancy loss.
8 + 15	Stephan Gordts		2323	Also hysteroscopy has been described as a rather invasive procedure (line 2323): we know that a diagnostic hysteroscopy nowadays is performed without anesthesia in an outpatient setting and is less painful than a HSG. As such this line gives an incorrect information and I suggest to remove it.	We stated that "The main disadvantage of hysteroscopy is the invasiveness of the procedure, although nowadays it can be performed (in an office setting) under local anesthetics". We added that it can be applied In an office setting
8 + 15	Stephan Gordts			General comments: as ESHRE has its own classification on uterine anomalies, this classification should be implemented in the RPL guidelines instead of the AFS classification. As such the term"arcuate" uterus and bicornuate is not existing in this classification and should also be avoided in the RPL guidelines. If ESHRE guidelines does not use ESHRE classification	We acknowledge that we had used the AFS classification as this is used in all included studies. We have now changed to the ESHRE/ESGE classification in the recommendation, and referred to the classification and diagnosis paper.

				is somewhat paradoxical and does not help the widespread diffusion of this new classification system.	
14	Raminta Bausyte	102	3152-3153	Till now it is unclear the optimal levothyroxine dosage required for woman with eventual hypothyroidism. It is necessary to specify the recommended levothyroxine dosage for woman with subclinical hypothyroidism or thyroid autoimmunity and RPL.	There is no optimal levothyroxine dose which can be recommended. Dose should be individualized based on TSH levels. We added the recommended trimester specific TSH levels to the text.
12	Raminta Bausyte	95	2935	I would like to offer to add revised Sapporo clinical and laboratory criteria for diagnosis of antiphospholipid antibody syndrome in 2006. Criteria for the diagnosis of the antiphospholipid antibody syndrome are shown in the article "*Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4(2):295-306. DOI:10.1111/j.1538-7836.2006.01753.x.*" *(attached article, p. 297, Table 2.).*	We have used the Miyakis criteria (from the article you quote) in the guideline, which are an update of the Sapporo criteria. A sentence was added to clarify this.
A	Raminta Bausyte	15	156-159	I would like to take look at a definition of pregnancy loss. *The National Center for Health Statistics, The Centers for Disease Control and Prevention, and the World Health Organisation* all define pregnancy loss as any pregnancy termination prior to 20 weeks' gestation or with a fetus born weighing below 500 g. These criteria are somewhat self-contradictory because the average weight of a normally developed 20-week fetus is 320 g, whereas a birthweight of 500 g is the mean for 22 to 23 weeks *(Moore KL: The Developing Human: Clinically Oriented Embryology, 2nd ed. Philadelphia, WB saunders, 1977)*. According to these definitions, technological and neonatal care development crossword and national clinical practice, I would like to suggest for consideration of a pregnancy loss definition as all pregnancy losses from the time of conception until 22 weeks of gestation. Furthermore, I would like to offer that a fetal birth weight of 500 g will be used to define viable pregnancy when gestation time is uncertain (e.g. irregular menstrual cycle, woman forgot the date of last menstrual period, developing countries).	The GDG feels that we have written a clear and detailed explanation for the definitions used for pregnancy loss and RPL, and we don't think it is relevant to add the 1977 WHO definition on pregnancy loss.
10	Alessandra Pipan	88-89	2700 2736	not very clear whether the number of previous miscarriages increases or decreases the chances of good outcome	More miscarriages results in a lower chance of good outcome. We have revised the sentences and feel this is clearly stated
??	Alessandra Pipan	82 147	2477 + …	among the recommended further studies , also effects of infections (chronic carrier state and immunogenicity)	The GDG has decided not to add this as a research recommendation

7	Alessandra Pipan	68	1954 all	no clear agreed definition on LPD makes it impossible to draw any conclusions . It's not clear if it's a real phenomenon and if yes, is it worth studying ?	We added a sentence to the discussion section; "Based on the current evidence, luteal phase insufficiency should not be the focus of future trials in RPL"
7	Alessandra Pipan	66	1924 and 1947	CCCT is cited whereas at the end of the paragraph it's being no more acceptable is pointer out	We listed all studies on ovarian reserve testing (all methods). In the justification, we explained the results and why we did not recommended testing.
7	Alessandra Pipan	65	1878 all	LOW levels of Prolactin (?) - (Li et al. I couldn't read the study — only 174 pts- maybe other factors ?	We specified that the other women had prolactin levels within the normal range (<660mIU/l).
12	Alessandra Pipan	44	1158 all	in the final recommendation ' evaluate the effect of hydroxychloroquine etc ' no mention in the chapter - nor biblio -The impact of hydroxychloroquine treatment on pregnancy outcome in women with antiphospholipid antibodies . Sciascia Talavera ???	I added a sentence on hydroxychloroquine referring to the research recommendation in section 12.2; Treatment for APS.
1	Alessandra Pipan	23	445	not only endometritis, but tubal infection /damage STDs related- w abnormal/ damaging milieu	Infection (in general) is outside the scope of the document. Chronic endometritis was part of the scope of the guideline and is included.
A	Alessandra Pipan	17	221-244	for the same above reasons RPL regarded as a different entity in respect to biochemical. (Biochem.Preg .during assisted concpt . J Clin Med Res 2013 Aug - Repeated Bioch PL Christiansen	We added a sentence on non-visualised pregnancy losses. Many of the NVPLs are losses happening between gestational week 6-12 where no ultrasound was done often because it was the patients' first loss(es).
A	Alessandra Pipan	16	201 202	biochemical pregns are part of the 25% of 'normal' PLosses and might represent a statistical bias also different cut offs for definition (see biblio next line)	We added a sentence on non-visualised pregnancy losses. Many of the NVPLs are losses happening between gestational week 6-12 where no ultrasound was done often because it was the patients' first loss(es).
0	Christiane Kling			Additional minor suggestions: P 8, recommendation 19: HLA-DRB1*07, HLA-DRB1*03 or HLA-DRB3*03? P 16, line 198: please correct: the P 31, line 753 ff: I suggest to provide an explanation: what is a drink, what is a unit of alcohol? P38, line 934: Embryonic causes are most prevalent, maternal factors are associations P49, Line 1306-1307: DRB1*15; -DQB1*0501/2 and -DRB3*0301/ chapter 6.2: current nomenclature for 4 digit alleles is *05:01, *05:02, *03:01 P 52, line 1378: please check: DRB1*03, DRB1*07, or DRB3*03? P 87, line 2703: 41.7% please check the sentence	We have corrected all errors in the text as suggested, and resolved the reported discrepancy by deleting "a known risk factor for a subsequent miscarriage" This sentence was used from the paper of Boots, and deleted as the chapter reports on obesity.

				P 99 line 3059 please correct “off” **Discrepancy:** p 29: line 673: …euploid miscarriage, a known risk factor for a subsequent miscarriage… p 37, line 934-935: No clear effect of genetic testing of the pregnancy tissue on prognosis (subsequent live birth) has been described Genetic results showed that unbalanced chromosomal aberrations are most prevalent in the early embryo. Infertility and the rate of embryonic aneuploidy seem to be linked with each other. Therefore it is likely, that losses in the 6th week or e.g. blighted ova reflect some degree of subfertility. Maternal contamination/overgrowth in culture is more likely when vital embryonic tissue is scarce, e.g. more frequent in early than in late first trimester losses. So when losses of a group of subfertile (e.g. obese) women are examined genetically, one would expect them to have more “normal” (female) results and a worse prognosis at the same time. Therefore euploid miscarriage is not a risk factor by itself but produced by a technical problem.	
17	Christian e Kling	122	Ch 17	17.1 instead of “immunotherapy”, please insert: “Lymphocyte immunotherapy (LIT)” (Remark: with appropriate awareness and precautions, LIT cannot be regarded a high risk therapy. In 20 years, no serious adverse effects have come to our knowledge despite distinctive counseling and follow-up. Our experience has been published and discussed. We applied the therapy before a further pregnancy was initiated.)	We changed the heading and added a sentence on the study of adverse events with injections with paternal lymphocytes based on Kling (HR 2006).
13	Christian e Kling	99	Ch 13	*Key question: Which therapeutic interventions should be offered to patients with RPL with suspicion of immunological background to increase live birth rate?* *OR Should therapeutic interventions be offered on the basis of suspicion of an immunological background?* Since no immunotherapy – except possibly for antiphospholipid syndrome - is of proven value, they are usually offered off-label. In my opinion, this means that possible teratogenicity by additional interventions of unproven value in early pregnancy is regarded acceptable for high-risk pregnancies, and that the couples have to bear this risk. I presume that this is not an issue the ESHRE working group would support.	In reply to this key question, we have outlined the absence of any relevant biomarkers and treatments. We do not recommend any treatments for patients with RPL with suspicion of immunological background. Most studies on immunotherapy have been assessed in women with unexplained RPL and we refer to chapter 17 for a thorough assessment of these treatments.

6	Christiane Kling	Ch 6		GMP: I suggest a statement that in reproductive medicine, quality standards for diagnostic tools are mandatory according to the principles of good manufacturing practice. Diagnostic standards which are based on ignoring laboratory rules and which are set by constant repetition in the literature do not need to be disproved by prospective trials. It would contribute to a clear guideline position in this respect if the issue of performing further trials would not be considered again.	We agree that that the guideline should stress that in reproductive medicine as well as other areas of medicine we need to set quality standards for diagnostic tests. This is in particular important regarding NK cell testing in the blood and endometrium of RPL women where standardization of methods is lacking
6	Christiane Kling	Ch 6		ANA should not be considered for explanatory purposes. In the absence of clinical symptoms (other than miscarriage!), antinuclear antibodies are no suitable screening assay for autoimmunity because it is well-described that the rate of unspecifically positive values is high. To my knowledge, PL´s are not a feature of any autoimmune diseases (apart from APS/ SLE). The test is not approved to indicate any kind of immune problem confined to the uterus. (I remember one 38 year old patient of our clinic with RPL and high ANA titres who apparently did not suffer from autoimmune disease but finally turned out to have metastatic breast cancer.) See: . American College of Rheumatology, Fast Facts: • A positive ANA test means autoantibodies are present. By itself, a positive ANA test does not indicate the presence of an autoimmune disease or the need for therapy. • ANA testing can produce a positive result without any actual disease process. https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Antinuclear-Antibodies-ANA	The situation regarding ANA testing is very similar to the situation regarding TPOabs testing, which is recommended in this guideline. Both ANA and TPOabs are found with increased prevalence in RPL and seem to display a negative impact on pregnancy prognosis. Neither TPOabs nor ANA have been proven directly to harm the fetus or trophoblast and no treatment has so far been proven to help women with these antibodies and RPL. Therefore the recommendations should be similar: ANA (and TPOabs) testing should be considered for explanatory purposes Concerning the Am Col Rheum fast facts: Both facts are also valid for TPO antibodies
6	Christiane Kling	Ch 6		Concerning histocompatibility I would have been very cautious for statistical reasons [4] E.g. HLA DRB1*03 and DRB1*15 are very frequent alleles found in 20-26% of the Caucasian population. The same applies to DRB3*03:01. Therefore, they quite unlikely have a negative impact on reproduction (See: http://www.allelefrequencies.net/). Where does the statement concerning DRB1*07 come from? It cannot be traced back to the explanatory text, but appears in the recommendations.	We agree that the HLA-DRB1 alleles having a negative impact impact on subsequent live birth rate in RPL have a high prevalence in the Caucasian population. However, a high population prevalence of a genetic polymorphism does not exclude the possibility that the polymorphism displays a negative impact on reproduction. An example: the HLA-DRB1*04:01 allele is the strongest genetic determinant of type I diabetes in Caucasians: carriers of

					this allele have an OR = 8 for being diagnosed with type 1 diabetes. In most type I diabetes patients, the disease is diagnosed before reproductive age. Until the introduction of insulin treatment 100 years ago, most patients with type 1 diabetes would die before reproductive age. However, 19.8% of Danish people carry the HLA-DRB1*04:01 allele in spite of its strong negative impact on reproductive fitness for hundreds of years. This seemingly paradox can be explained by "antagonistic pleitropy", that is a genetic variant having several effects where some increase and some decrease reproductive fitness, which countrerbalance each other (Stearns and Medzhitov: Evolutionary Medicine, Sinauer Associates Inc). Some of the HLA alleles predisposing to autoimmune diseases (and RPL) may provide increased resistance to infections helping to maintain their high prevalence in the population. The reference to HLA-DRB1*07 comes from the paper by Kolte et al. We added the study to the evidence section, but as the association with HLA-DRB1*07 is weaker, we erased it from the recommendation.
6	Christian e Kling	Ch 6		As in preceding guidelines, various immunological approaches are recapitulated. It may be worth mentioning that there is a strong historical dimension in them dating from the 1980ies where idiopathic RPL were thought to be caused by immunological disturbances of the mother or interaction of the embryonic and maternal tissue (transplantation immunology, cytokines, "autoimmune pregnancy loss" and NK cells). The way from a mouse model or other assumptions in science to introduction into clinical practice was held very short. Another shortcut was made by extrapolating findings from peripheral blood to the uterine milieu (NK cells). Thirdly, technical limitations may have been underestimated. Until now, it is very difficult or impossible to transform functional results from a research setting into a stable functional assay on immune cells for diagnostic purposes (e.g. regulatory T-cells). There is little awareness that genotyping is no solution because it does not tell anything about the actual expression and regulation of the respective molecules on the cell surface (e.g. KIR). A.	In the final part of section 6.5 we have already addressed the problems concerning measurement of NK cells, which render this test unfit for clinical use at the time being to quote: "there are significant technical challenges; the frequencies of NK subsets between the endometrium and peripheral blood are extremely different"; "technique is prone to subjective evaluation and surface marker expression change due to enzymatic digestion" ; "blood NK numbers fluctuate hugely in the menstrual cycle." and "measurement of uterine NK cells is also unfit for clinical practice due to lack of consensus about ranges of normal value and lack of standardization". The issue of KIR and HLA-C typing was addressed in Section 6.2 about HLA. We added a sentence in line 1393: "Due to the contradictive findings concerning KIR

				Moffett (same working group as S. Hiby) therefore has repeatedly pointed out that KIR genotyping is not suitable for diagnostic or even therapeutic purposes at present [1;2]. In order to establish new and valid diagnostic parameters, it would have been necessary - to reproduce results in the same or (even better) another lab - to evaluate mean values and ranges in a sufficiently numbered control (at least 50-100 individuals, maybe even more in the context of reproduction) before defining pathologies. - to clearly differentiate between various cell compartments, genotype, phenotype, and function I am not aware of any study which induced such a process before speculating on results. As far as NK cells are concerned, normal values in peripheral blood usually range from 2% to 27% [3], but in the context of reproduction, values were regarded elevated over 12-18%. This was psychologically disastrous for numerous women who learnt that their "killer cells were elevated" although their values were absolutely normal and their relative numbers in peripheral blood cannot be correlated to function of NK cell subpopulations harboured in the endometrium/ decidua anyway.	genotyping in couples with RPL, KIR and HLA-C typing is not suitable for diagnostic and therapeutic purposes at present" We also included this in the justification table.
17	Shehnaaz Jivraj	124	3861	Typographical error 40%	corrected
14	Shehnaaz Jivraj	106	3259	typographical error, should read .....too limited to	Corrected
8	Shehnaaz Jivraj	79	2388	In regard to 'MRI is not recommended for the assessment of uterine malformations in women with RPL.' Suggested would be MRI is not recommended *as first line* for the assessment of uterine malformations in women with RPL.	We have changed this recommendation, now stating that MRI is not recommended as first line option, but can be used when 3D US is unavailable.
7	Shehnaaz Jivraj	69	2007	typographical error in nog/t	Corrected
7	Shehnaaz Jivraj	63	1820	should read PCO morphology and not PCOS morphology	Corrected
5	Shehnaaz Jivraj	44	1142	This recommendation is too succinct for such a broad range of pregnancy losses that can occur. While there may be validity in the statement for RPL in the first trimester, there may be a case for screening for inherited thrombophilia following pregnancy loss in the second or third trimester or	This recommendation is in agreement with the recommendation of the American College of Chest Physicians: "For women with a history of pregnancy complications, we suggest not to screen for inherited

				as the guideline describes as secondary RPL. This has been corroborated by traditional studies like the EPCOT study by Preston et al (1996), not mentioned in the guideline. If the guideline wants to recommend only screening for inherited thrombophilia for research purposes, this should be clarified that it refers to first trimester RPL only and where no other risk factors such as a personal or family history of venous thrombo-embolism exist. Short and succinct statements that generalise management, will reduce the reader's confidence in the guideline if exceptionality is disregarded.	thrombophilia (Grade 2C)". We added a sentence to the recommendation.
5	Shehnaaz Jivraj	42	1139	To my knowledge, in regard to the second MTHFR mutation studied, this should be 1298 and **not** 1286	Both papers mentioned reported different mutations: Hickey(2013) mentions A1286C, while Chen (2016) tested A1298C. We have corrected the sentence accordingly
5	Shehnaaz Jivraj	42	1089-1092	The reader of this review is likely to want to know the source data so vividly mentioned. Unfortunately no references have been provided. It is strongly advisable to provide references to source data as exact OR and CI have been quoted.	The data are from the review of Bradley 2012 which is mentioned at the start of the paragraph. We repeated the reference for clarity.
4	Shehnaaz Jivraj	37	930	.....should this read 'aneuploid' ? Or Line 931 .....fail to reveal	We have corrected this to "aneuploidy" in the second sentence.
1	Shehnaaz Jivraj	25	501	I do not agree with this blanket statement. These guidelines will be used to make decisions on resource allocation for supportive care and such a blanket and candid statement could be misinterpreted by individuals not au fait with RPL research. It could have a negative impact on resource allocation for supportive care and stress management in unexplained RPL. Would it not be better to say, ' stress may be associated with RPL but it is still unclear if this is a direct cause of PL.'	To address this comment, we have rephrased this recommendation: Stress is associated with RPL, but patients should be informed that there is no evidence that stress is a direct cause of pregnancy loss.
A	Shehnaaz Jivraj	5,16	135, 202, 203	Line 202 and 203 contradict line 135 on the issue of including molar and ectopic pregnancies as RPL. It needs clarification.	There was an error in line 203: we changed "excluded" to "included" to correct this: If identified as such, ectopic and molar pregnancies should not be included in the definition.
A	Shehnaaz Jivraj	15	174	probability of carrier status Clarify please. Is this carrier status of a chromosomal abnormality?	We clarified this by adding "(of a structural chromosomal abnormality)" in the sentence
A	Shehnaaz Jivraj	15	160-163	In regard to 'The distinction between primary and secondary recurrent pregnancy loss can be made. Primary RPL is described as RPL without a previous ongoing pregnancy (viable pregnancy) beyond 24 weeks' gestation, while secondary RPL is defined as an episode of RPL after one or more previous pregnancies progressing beyond 20 weeks' gestation. '	We corrected this error to 24 weeks in the definition of secondary RPL.

				This leaves a gap in definition between 20-24 weeks. If someone has had 2 PLs at 22 weeks, is this primary or secondary? It needs a clear cut gestational age if we are going to define primary versus secondary.	
14	Shehnaaz Jivraj	11		In regard to 'Pituitary suppression before induction of ovulation in women with RPL and PCOS could be an option to reduce the risk of PL.' On the one hand the guideline reads that OI could reduce RPL but on the other hand the rationale states that evidence is too limited. Clarification is needed if this is in the context of unexplained RPL or anovulatory infertility plus unexplained RPL.	There is insufficient evidence to recommend OI in RPL without PCOS. In women with PCOS and RPL undergoing OI, prior pituitary suppression could be an option. This was clarified in the justification. We deleted the recommendation.
12	Shehnaaz Jivraj	10		In regard to 'For women with inherited thrombophilia and a history of RPL, we suggest not to use antithrombotic prophylaxis unless in the context of research.' Suggest adding that…. unless thromboprophylaxis is indicated for VTE prevention	We added this exception to the recommendation (line 2930)
8	Shehnaaz Jivraj	9		In regard to 'MRI is not recommended for the assessment of uterine malformations in women with RPL.' This may mislead the reader into negating the role of MRI altogether, if the reader did not read the small print that reasons out that MRI is not recommended because 3D USS is better. This would serve better to read, 3D USS is superior to MRI in the assessment of uterine malformations in women with RPL. However, where 3D USS is not available, MRI is helpful to assess uterine morphology as a second line to 2D USS especially in assessing fibroids and surgery planning.	We have changed this recommendation, now stating that MRI is not recommended as first line option, but can be used when 3D US is unavailable.
0	Arianna D'Angelo		1390 1450 3206 3261	Some controversial treatments or unusual tests like intralipids or MTHFR are clearly explained but others (cytokines, NK cells; metformin;bromocriptine) are not explained and there is straight the explanation of the evidence. It would be good to be consistent through the whole guidelines, either are explained or not.	We acknowledge that different authors for different chapters may have led to inconsistencies. We have tried to improve this.
14	Arianna D'Angelo	Chapter 14		To define normal cut off for TSH? <2.5	We added a sentence on this is in section 14.1: TSH levels should be compared to local trimester-specific reference ranges, or recommended upper limits: first trimester, 2.5 mU/l; second trimester, 3.0 mU/l; third trimester,3.5 mU/l. (Lazarus 2014).
2	Arianna D'Angelo	783		define what are soft drugs	The definition of soft and hard drugs depends on its risk of dependency, and legal status. We added cannabis as an example to clarify.

0	Arianna D'Angelo	198		Spelling: the	Corrected
A	Arianna D'Angelo	188 - 190		It does not give a nice message. If there is disagreement and it is so clearly and openly defined I think this weaken the definition. This point should be reconsidered if not removed. Please further clarify if implantation failure is included or not.	We agree that the discussion weakens the definition, but we chose to be transparent on the opinions, rather than not having a definition. We have added a statement on implantation failure.
17	RCOG Guidelines Committee		3949	Does progesterone supplementation by any other route (other than vaginal) provide any benefit in women with RPL? This needs to be clarified here otherwise some might use oral progesterone.	For the individual studies we specified whether they used oral or vaginal progesterone were used. In the justification, we mention that vaginal P is not useful, and oral P needs further studies.
17	RCOG Guidelines Committee		3791	In the context of infertility treatments and ART, recent evidence from the ESHRE Study Into The Evaluation of Oocyte Euploidy by Microarray Analysis (ESTEEM) (Preliminary results presented at the recent ESHRE 2017 annual meeting) suggests that Pre-implantation Genetic Screening (PGS) reduces the risk of miscarriage, however it does not improve live birth rates. Consider including this as a statement in the guideline, i.e. current evidence suggests that in-vitro fertilisation with PGS does not improve live birth rates in women with unexplained RPL.	We have described PGS as a treatment option in the genetics chapter (chapter 11) and decided not to repeat this n the chapter on unexplained RPL.
14	RCOG Guidelines Committee	107	3304	Vitamin D supplementation to start from which gestational age and how long should it be continued?	We added some text on the dose and pregnancy period of use based on the review of De Regil 2016.
7	RCOG Guidelines Committee		3253	On page 65, line 1872, assessment of PCOS is not recommended. So this recommendation in line 3253 remains unclear. How can we identify those women who might need pituitary suppression before induction of ovulation?	A good point, we are inconsequent here. We have removed the recommendation and stated it as a conclusion.
7	RCOG Guidelines Committee	102	3152-3	What does eventual hypothyroidism mean?	We deleted “eventual” as this was an error.

7	RCOG Guidelines Committee	102	3150-2	Recent (2017) American Thyroid Association guidelines recommend a lower cut-off TSH limit of <2.5 for women with infertility in order to reduce the risk of miscarriage (moderate evidence). The authors suggest thyroid screening with TSH and TPO antibodies. However the data that is presented states that 1. there are no studies evaluating the effect of treatment on pregnancy outcomes in women with RPL and thyroid autoimmunity 2. meta-analyses haven't shown a statistical reduction in risk of miscarriage in euthyroid women with thyroid autoimmunity (RR 0.52 but CI 0.22-1.15) Therefore identifying women who are TPO positive but not clinically hypothyroid doesn't really seem to confer any benefit as treatment hasn't been shown to work.	We have revised the ATA guideline, and the lower cut-off TSH limit was not recommended for preventing miscarriage, but for improving the outcome of ART treatment. Therefore, we decided not to change the guideline
12	RCOG Guidelines Committee		2937-83	The recommendation in this section says that heparin and aspirin should be considered in women with APS and a history of 2 or more pregnancy losses. The supporting text (lines 2986 – 2988) says that 'the existing evidence suggests that a combination of heparin … and aspirin improves LBR in women with APS and RPL (three or more PLs, no evidence for two or more PLs). The recommendation has to reflect the evidence and the supporting text (which it doesn't do here).	We have changed the recommendation to three or more PL, to make it consistent with the justification
12	RCOG Guidelines Committee	95-6	2937-61	Most clinicians wouldn't use UFH now due to the risks associated with its use in pregnancy Think this is a GPP as there is evidence that treatment of women with APLS with heparin and LDA doesn't improve outcomes in pregnancy (TIPPS study Lancet 2014). I think the recommendation has to suggest that the benefit of heparin and LDA (if it exists) is debatable and the patient should be given the option of treatment or no treatment	The recommendation formulated on this is a conditional recommendation based on very low evidence. The recommendation also states we "suggest" treatment, rather than "recommend" treatment. As a rule, conditional recommendations are the starting point of discussion with patients and shared decision making, which is suggested by the reviewer.
12	RCOG Guidelines Committee	94-5	2929	Please consider the evidence from one prospective RCT to suggest the use of low molecular weight heparin in women with 2nd trimester miscarriage (Gris C, Mercier E, Quéré I, Lavigne-Lissalde G, Cochery-Nouvellon E, Hoffet M, et al. Low-molecular weight heparin versus low-dose aspirin in women with one fetal loss and constitutional thrombophilic disorder. *Blood* 2004;103:3695–9).	In our evidence synthesis, we have focused on RPL and only extended to miscarriage if no evidence was found. For this topic, we did not extend the literature search to Miscarriage or single fetal loss.

0	RCOG Guidelines Committee	86	2632-719	This is a duplication of Section 3 881-882. What is the value of repeating this in a slightly different form?? This was a recurrent theme throughout the guideline and streamlining of the recommendations may reduce the size of the document overall and make the reading and taking forward of the recommendations easier	The document was written to have each chapter as a stand-alone text. We will check and remove any repetitions
8	RCOG Guidelines Committee	77-80	2300-75	3D gynae ultrasound and sonohysteroscopy isn't readily available in all units at present. What do the authors suggest under these circumstances? MRI?	3D ultrasound is becoming more and more available. However, based on the reviewer comments, we acknowledge that we should have elaborated on what to do in the absence of 3D US; We changed the statement on MRI.
6 NK	RCOG Guidelines Committee	54-5	1496	Might the recommendation be slightly more specific – e.g. NK cell testing of either peripheral blood or endometrial tissue is not recommended in women with RPL	We added the suggested specification to the recommendation
6 hla	RCOG Guidelines Committee		1378	Recommendation. HLA class II determination in secondary RPL after male childbirth: this could mean that almost half of all secondary RPL s will be subjected to HLA class II determination. Given the information in the previous page line 1342 to 1351, and in the following page lines 1385 to 1389, do we have enough evidence to make this a recommendation?	Although only one study has been published on the impact of HLA-DRB1 in women with secondary RPL with a firstborn boy this study was large, and there was a strong dose-response effect: patients with two "risk" HLA-DRB1 alleles exhibited a highly significantly poorer prognosis than those with "only"one risk allele" who did much worse than those with zero risk alleles. We have added that the recommendation is only valid in North European populations since HLA associations are specific for ethnic groups.
4	RCOG Guidelines Committee	39	994	I'm not clear what this recommendation means the way that it is written. Do the authors mean that in couples where one of the parents is a translocation carrier, couples should be advised that the chance of a live birth is good (71% in 2 years)? Also when I have a patient with a translocation and recurrent fetal losses I would refer to genetics for a further discussion of risk. My understanding is that the risk of recurrence is individualised for each patient based on family history and obstetric history and the particular translocation. I don't think this statement is helpful in counselling couples about the risks in future pregnancies	In the treatment chapter (11.2) we recommend (as suggested) that All couples with results of an abnormal fetal or parental karyotype should receive genetic counselling, and that they are informed of possible treatment options. This was not added to the diagnostic chapter. The recommendation on prognosis was added to the text

				Stengel-Rutkowski S, Stene J, Gallano P. Risk estimates in balanced parental reciprocal translocations: Expansion Scientifique Française, Paris; 1988. Stene J, Stengel-Rutkowski S. Genetic risks of familial reciprocal and Robertsonian carriers. In: Daniel A, editor. The Cytogenetics of Mammalian Autosomal Rearrangements. New York: Alan R Liss; 1988. p. 3-72. Midro AT, Stengel-Rutkowski S, Stene J. Experiences with risk estimates for carriers of chromosomal reciprocal translocations. Clin Genet 1992;41(3):113-22. Jalbert P, Sele B, Jalbert H. Reciprocal translocations: a way to predict the mode of imbalanced segregation by pachytene-diagram drawing. Hum Genet 1980;55(2):209-22. Jalbert P. [Genetic counseling in reciprocal translocations]. J Genet Hum 1988;36(1-2):3- 14. Borgaonkar D. Chromosomal Variation in Man. *A Catalogue of Chromosomal Variants and Anomalies*. 8th ed. New York: Wiley-Liss; 1997.	
4	RCOG Guidelines Committee		939	This recommendation needs to be more specific please. When and for which couples is karyotyping or genetic testing of conceptus and/or parents necessary?	The GDG has judged that there is insufficient evidence of the usefulness of genetic testing with regard to treatment and prognosis, in general. Based on the existing evidence, it is unclear which couples would benefit from testing.
4	RCOG Guidelines Committee		927-32	This paragraph needs clarification or the wording may need to be changed to make the meaning clear.	This paragraph revised based on other comment
4	RCOG Guidelines Committee		902-57	It is my understanding (and personal experience) that karyotyping of the pregnancy tissue may be of use if an unbalanced translocation is identified – this may result in one or either parent being identified as having a balanced translocation. I am not sure that the explanation given in paragraph 986-992 is good reason not to do the testing (ie significantly more carrier couples may choose not to try for another pregnancy).	We added “a translocation in the pregnancy tissue” as a factor in the risk assessment prompting parental karyotyping. We do not state that the observation that couples may decide to stop trying Is a reason for not performing parental karyotyping, and have rephrased the sentence to clarify this.
3	RCOG Guidelines Committee		875-7	This section is a bit unclear - Is parental karyotyping relevant for 3 or more pregnancy losses or mother’s age <39 years?	We rephrased the sentence.
2	RCOG Guidelines		856	Text says that studies have suggested an impact of the use of soft drugs on the risk of RPL; yet earlier in the guideline (lines783 – 784) it is stated that	We have deleted “soft drugs” in line 856 as this was indeed not consistent with the earlier statement.

	Committee			'we found no evidence that using soft drugs could be a risk factor for pregnancy loss in women with RPL'. Document needs to be consistent throughout.	
1	RCOG Guidelines Committee		783	Please clarify what is meant by 'soft drugs'	The definition of soft and hard drugs depends on its risk of dependency, and legal status. We added cannabis as an example to clarify.
1	RCOG Guidelines Committee		734-44	No conclusion was given in this section on Health Behaviour modifications as to whether exercise had an impact or not.	We have decided not to formulate any conclusion to the section on exercise, lifestyle behavior and other sections, rather than repeating that no conclusion can be drawn.
1	RCOG Guidelines Committee		483-502	The recommendation states that 'patients should be reassured that there is no evidence that stress causes pregnancy loss'; the supporting text above does show an *association* between RPL and stress and there is a small study (Nepomnaschy et al 2006) that did show that increased stress during pregnancy was associated with pregnancy loss. I think the recommendation should not be so emphatic.	To address this comment, we have rephrased this recommendation: Stress is associated with RPL, but patients should be informed that there is no evidence that stress is a direct cause of pregnancy loss.
A	RCOG Guidelines Committee	16	204	Does "Recurrent early pregnancy loss" carry different connotations and implications? If not then what is the reason for identifying them as a separate entity?	We have indeed not formulated any recommendations specific for REPL. However, the term is used in several studies.
A	RCOG Guidelines Committee	16	202-3	Does it mean that 2 consecutive ectopic gestation and/or molar pregnancies will be defined as recurrent pregnancy loss (RPL)? These could well have completely different etiology than what applies to other RPLs. Including these entities within the definition will instigate time consuming and often unnecessary investigations.	There was an error in this sentence which is now corrected: ectopic and molar pregnancies are not included in the definition
A	RCOG Guidelines Committee	15	173-4	"……that there is no difference in the probability of carrier status between couples……" Carrier status of which abnormality? Please clarify.	We clarified this by adding "(of a structural chromosomal abnormality)" in the sentence

9	RCOG Guidelines Committee	10 & 83		There is increasing evidence to suggest an association between DNA fragmentation and RPL. However, the technology is not reliable and reproducible at present and it cannot be used in a cycle of assisted reproduction treatment. In addition there is lack of cost-effective interventions that are proven to improve outcomes. Therefore routine testing outside of research shouldn't be recommended at present.	Given the potential of this association and the absence of previous inclusion of advice for partners of women experiencing RPL, the benefit is to provide a partner risk assessment alongside the more established female profiles. The evidence from the 2 meta-analyses in 2013 is that a doubling of the risk of miscarriage with sperm DNA fragmentation. In the absence of a more proven test, the conditional recommendation of assessing sperm DNA fragmentation in couples with RPL is given as conditional and 'can' rather than 'should' can be considered.
A	RCOG Guidelines Committee	6	152	The definition of RPL is not in line with guidance from other organisations including the RCOG. However, the authors acknowledge the disagreement of some guideline group members and that other bodies/clinicians might choose to keep the definition of 3 or more consecutive losses. Given the committee's difficulty in agreeing a definition, might the definition be revised to reflect this e.g. 'A diagnosis of Recurrent Pregnancy Loss (RPL) can be considered as the loss of two, or three, pregnancies.' To start investigations after 2 miscarriages would be a major change in UK practice with resource implications. The scope of the ESHRE guideline does not distinguish between 1st or 2nd trimester losses.	Thank you for this comment, but the GDG has decided not to change the definition of RPL.
0	RCOG Guidelines Committee	6-14		There are many abbreviations that have not been explained in this section. Given that many if not most readers might only refer to this section it would be advisable to explain all abbreviations within this section. Example : GDG, CGH, LBR, LA, ACA, HLA, TSH, TPO, SCH, PCOS, UFH, LMWH, G-CSF etc.	We have explained all abbreviations in the summary chapter
0	RCOG Guidelines	General	General	There are a few typo errors in the document: e.g. line 198 "…by the doctor and eth (the) couple…" spelling of THE line 202 has repetition of).). line 713 'or' should be 'of'	Corrected

	Committee				
0	RCOG Guidelines Committee	General	General	Thank you for asking us to review this guideline. The document is well written if rather lengthy. The summary points are helpful.	Thank you. Positive feedback – no action needed.
4	Ahmet Berkiz Turp	37	899	Screening for Genetic Factors This part mentions only pregnancy tissue screening and peripheral maternal and paternal karyotype screening. The maternal and paternal karyotyping is screened from peripheral lymphocytes which are developed from cells that divides by mitosis. However, fetus is made up of 2 gametes which is divided and developed for meiosis cell development. So, we must look for gametes karyotyping that is oocyte and spermatozoa karyotyping. Oocyte karyotyping is difficult to look for karyotyping but Sperm karyotyping can give us some clue about genetic abnormality which is developed by paternal genetic transition. This can be done by sperm FISH or other gamete genetic testing. So, in future we must include some gamete genetic screening to recurrent pregnancy loss to this guideline (1) Reference:http://new.isgesociety.com/wpcontent/uploads/isge2010/abstracts/Turp_21.pdf	oocyte and spermatozoa karyotyping was outside the scope of the guideline. It will be assessed for relevance when an update of the guideline is started.
8 + 15	ESHRE/ESGE CONUTA Group			Additional Comments - Carlo De Angelis Appreciate all the comments that Attilio Di Spiezio Sardo did. It's not acceptable after more than 5 years of efforts for the proposition and wide spread of the new ESHRE/ESGE classification to read an ESHRE draft where the AFS classification is the standard. Secondly, it should be emphasised that the diagnosis of a CUA is an integrated diagnosis, since every single tool we take into account is phisician- dependent (it is true for 3D US, MRI and Hysteroscopy). Too many times in our clinical practice we match with not-trained sonographers as well as hysteroscopists or radiologists and the pathology is misdiagnosed if a second level examination is not performed. Finally, If it's true that Hysteroscopy is still considered the gold standard, eventhough associated to laparoscopy, it cannot be completely neglected for the diagnosis of CUA, assuming a fake dogma that "....it is still too	We have adapted the terminology to the ESHRE/ESGE classification, except when referring to paper published before the classification. We agree that the diagnostic tools depends on physician's experience and technique's availability. We cannot include in the guideline a circumstance like «the ultraonographer is not well trained», but we have added a sentence stating that local availability and experience could be relevant in selecting the diagnostic approach. With regards to the comment on hysteroscopy, we agree that hysteroscpy and laparoscopy is the gold standard, because of direct visualization, but we also have to add that they are invasive. The GDG believes that invasive

				invasive". People who deliver these concepts demonstrate at least an uncertain knowledge of the issue.	techniques are not necessary most of times to reach a correct diagnostis.
8 + 15	ESHRE/ESGE CONUTA Group			Additional Comments - Caterina Exacoustos I completely agree with your comments and probably I will be less diplomatic and ask more clearly to change this chapter (who wrote it?). The citation of old papers is non acceptable after all the work we do for our guidelines. Despite Saravelos paper in an excellent analysis, it is date 2008, most of the study used had only an hysteroscopic evaluation and not 3D therefore there is an uncertain diagnosis of septate or arcuate uterus. Finally I am not sure that hysteroscopy and laparoscopy is actually the gold standard in the diagnosis of CUA, I also not agree that SHG and is so highly accurate can replace LPS, I do not believe in Ludwin study. Finally regarding the treatment nothing is mentioned on T-shaped uterus and nothing about bicorporal septate uterus And finally the most important is to stress the arcuate uterus of the AFS classification without any definition at hysteroscopy only subjective evaluation and only 3D gave a definition with Salim classification 2003, measuring an angle without any measurements of myometrium and septum thickness. How many arcuate uterus were treated with metroplasty in the past (and used for published studies) and probably were septate uterus? I think that this ESHRE guideline must stress this concept: now the diagnosis with 3D is more accurate and we must start again to define what is abnormal and should be to treated and what is normal and need no treatment. Attached also the ESHRE PDF with my comments in yellow	We thank this reviewer for her personal opnion, but we attempted to base our opinion on available studies (which were assessed for quality before inclusion). A meta-analysis, although of 2008, is of higher scientific quality than a consensus document when discussing the accuracy of different techniques. The comment on the absence of recommendations for the treatment of T-shaped and bicorporal septate uterus is correct. We acknowledge that there are a lot of uterine malformations and we focussed on those that are more frequent and that have been described in the context of RPL. We have refrained from formulating recommendations on small studies and case reports, as on this topic, they were insufficient to support relevant clinical advice. We added a sentence on the absence of studies in the text. The comment on arcuate uterus of the AFS classification is correct. The guideline recommends that use of 3D US. We have changed the recommendation on MRI. We hope that universal diagnosis with 3D US and MRI can improve knowledge on CUA, and on CUA in RPL patients.
8 + 15	ESHRE/ESGE CONUTA Group			Additional Comments - Nazar Amso I echo your comments and those made by other colleagues. It was good that they made reference to the ESGE/ESHRE consensus documents, most certainly from the "The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies" in Section 8. The extract text below from page 79 of the guidelines has flaws. The first highlighted text refers to a 2007 and 2008 papers from "? Gynaecology units", which would most likely be based on work that might	After reviewing the evidence and this and other comments, we still recommend 3D US as a firstline option. However, we decided to change the recommendation on MRI, now stating that MRI is not recommended as first line option, but can be used when 3D US is unavailable. (based on lower accuracy and higher costs compared to 3D US).

				have been done at least two years earlier (i.e. 11 or 12 years ago). Ironically, there is earlier evidence probably from Radiology departments that suggests the opposite! I attach a PDF of a PowerPoint presentation from a 2009 ESHRE Campus meeting in Manchester. Surely, science has progressed even further since then! Colleagues who have dealt with Mullerian Ducts Anomalies for a number of years would have experienced that MRI offers greater accuracy where complex malformations exist and it helps to plan treatment if appropriate. A categorical statement (second and that it is not recommended is NOT Scientific. More so, it cannot be "Strong" when based on incomplete evidence and cost. *ESHRE Proposed Guidelines 2017/2018* 2347 Magnetic resonance imaging (MRI) has been proposed as an optimal test that allows a simultaneous assessment of the cavity and fundus of the uterus, although controversy exist in whether MRI can replace combined hysteroscopy and laparoscopy (Chan et al., 2011). The accuracy and practicality of MRI has not yet been determined for the diagnosis of uterine malformations (Oppelt et al., 2007, Saravelos et al., 2008). MRI can be used to extend the examination to the abdomen, which could be helpful in the detecting renal anomalies that are frequently associated with uterine malformations Oppelt et al., 2007, Hall-Craggs et al., 2013). In a study of 202 patients with uterine malformations (not RPL), 36% of the women had associated abnormalities, mostly renal, but also cardiac, skeleton and neurological abnormalities were detected (Oppelt et al., 2007). These studies indicate a role for MRI in diagnosing renal and urological abnormalities associated with congenital uterine anomalies that may become clinically relevant in pregnancy. Another recent study suggest ultrasound for screening and MRI or CT (computed tomography) scan for confirmation of congenital anomalies of the kidneys and upper urinary tract (Ramanathan et al., 2016). MRI is not recommended for the assessment of uterine malformations in women with RPL. Strong ⊕⊕□□	

				highest sensitivity and specificity for diagnosing congenital malformations. Based on the higher costs and the absence of a diagnostic benefit compared to 3D US, MRI is not recommended. ESHRE Campus 2009 "MRI has been shown to be an accurate and non-invasive method for the evaluation of MDAs.(9,10) MRI is also helpful in elucidating the etiology of obstructed MDAs and is particularly useful in patients in whom surgical unification is anticipated.(11,12) 9. Reuter KL,et al. Septate versus bicornuate uteri: errors in imaging diagnosis. Radiology 1989;172:749-752 10. Mintz MC, Thickman DI, Gussman D et al. MR evaluation of uterine anomalies. AJR 1987;148:287-290. 11. Carrington BM, Hricak H, Nuruddin RR. MRI evaluation of Müllerian duct anomalies. Radiology 1990;176(3):715-720. 12. Letterie G, Haggerty M, Lindee G. A comparison of pelvic ultrasound and magnetic resonance imaging as diagnostic studies for Müllerian tract abnormalities. Int J Fertil Menopaus Stud 1995;40:34-38.	
15	ESHRE/ESGE CONUTA Group		3472-3473	It is stated "In women with RPL that are diagnosed with arcuate uterus during pelvic ultrasound examination, the effect of surgical removal is controversial and metroplasty is not recommended (Makino *et al.*, 1992, Giacomucci *et al.*, 2011, Jaslow, 2014)". The report on arcuate uterus should be probably deleted. It is not included anymore as a category in the ESHRE/ESGE classification, its AFS definition is functional and totally subjective with more than five described options in the literature and as stated even in AFS "definition" it should be considered as a septate uterus with normal function. Thus, the inclusion of any statement on that AFS category should be avoided. (see additional comments from the members of the group).	We have deleted the sentence on arcuate uterus as suggested
15	ESHRE/ESGE CONUTA Group		3468-3470:	Laparoscopic unification of a didelphys uterus has been described from some groups. However, its efficiency in improving life birth rates is unclear as stated. It might be useful to change the phraseology form "In women with RPL and didelphic uterus, laparoscopic metroplasty can be considered for improving live birth rate, although the effectiveness is unclear as the data are based on few studies and few patients" to "In women with RPL and bicorporeal uterus and double cervix (former AFS didelphys uterus) laparoscopic unification of the uterus has been described. However, the	Rephrased as suggested

				effectiveness of that intervention for improving live birth rates is unclear as data are based on few studies and few patients."	
15	ESHRE/ESGE CONUTA Group		3462	Endoscopic treatment of unicorporeal uterus is not feasible, thus, endoscopic reconstruction of this anomaly is not available. Only in cases of unicorporeal uterus with rudimentary horn and cavity, laparoscopic removal of the rudimentary horn with a cavity to avoid "ectopic" pregnancy in this cavity should be considered and in some cases hematocavity (obstructive symptoms). Thus, the statement "For unicornuate uterus, uterine reconstruction is not recommended" might be useful to be changed as follows "For unicorporeal uterus uterine reconstruction is not feasible. The prophylactic removal of a rudimentary horn with cavity might be considered".	We reformulated the recommendation as suggested
15	ESHRE/ESGE CONUTA Group	15.1		Congenital uterine anomalies Septate uterus A descriptive review of selected studies was done although in Annex 8 an evaluation of those studies is presented. The only existing meta-analysis (Venetis et al, 2014) evaluating the studies comparing reproductive and obstetric outcome of patients who had and had not undergone hysteroscopic resection of a uterine septum, and showing that "hysteroscopic removal of a septum was associated with a reduced probability of spontaneous abortion (RR 0.37, 95% CI 0.25 to 0.55) compared with untreated women" was not taken into account. The only publication after this meta-analysis with the same study question is that of Sugiura-Ogasawara et al (2015) having also a conclusion in the same direction. Despite the limitations (see also the meta-analysis of Venetis et al) in the existing publications, the currently available evidence supports the notion that hysteroscopic treatment of septate uterus is indicated in women with history of pregnancy losses. It is important to be noted that the recently published ASRM practice guidelines (Pfeifer et al, Fertil Steril, 106: 530-540) and the Updated NICE Guidelines (January 2015) recommend the hysteroscopic treatment of septate uterus in women with recurrent pregnancy losses (Level C).	We added the conclusion on metroplasty for septate uterus from the Venetis 2014, but this meta-analysis did not focus on RPL. The recommendations from other societies show (level C evidence) that there is very little evidence supporting a recommendation for hysteroscopic septum resection. The judgement of the GDG is based on possible harm and no good evidence of benefit, and it was decided not to modify this. It should be noted that the recommendation does not recommend against hysteroscopic septum resection.

				Thus, the proposal is to change the recommendation to as follows: "*Hysteroscopic metroplasty might be considered for women with RPL who have a septate uterus (Level C)".* Otherwise, there is no meaning also to recommend the evaluation of uterine anatomy with 3D US in women with RPL to diagnose a potential uterine anomaly (see previous recommendations)	
8	ESHRE/ESGE CONUTA Group			*Diagnosis of congenital uterine malformations* The main conclusions and the recommendations are in the same line as those in the "Thessaloniki consensus on diagnosis of female genital anomalies" (Grimbizis et al, 2016). However, those are mainly based on the important meta-analysis of Saravelos et al (2008) and some selected studies concerning the diagnostic accuracy of the different diagnostic techniques. However, an updated meta-analysis of all the published studies examining the diagnostic accuracy of all the available techniques in the diagnosis of CUA (having as "gold standard" for comparison laparoscopy and hysteroscopy) was included in the "Thessaloniki consensus on diagnosis of female genital anomalies". It should be also noted that Saravelos, who was member of the CONUTA group, took part in the update. Thus, it might be useful for the completeness of the Guidelines to include data from that ESHRE document instead of selected studies. It might be also useful to change the statement from "Imaging for detection of uterine malformations has been performed with a range of different techniques, all with different potential and limitations for diagnosing the various types of malformations, and *without consensus on the gold standard in diagnosing uterine malformations*" to "…. and an ESHRE consensus including recommendations for their diagnosis was recently published" (lines 2317-2319). This will also give the impression that the one ESHRE document is consistent to the other. In the recommendations terminology might be also useful to be consistent with the in ESHRE/ESGE terminology (line 2385 "…. and can distinguish between septate and bicorporeal uterus").	Saravelos et al is the most recent meta-analysis on the topic; the consensus is helpful, but not a systematic review (no methodology, expert opinion paper); We have added a sentence on the Thessaloniki consensus as suggested (An ESHRE consensus for diagnosis of congenital uterine anomalies was recently published {Grimbizis, 2016 #3410}.)
8	ESHRE/ESGE CONUTA	8.1		8.1 Anatomical investigations / Congenital uterine anomalies Evidence	We have replaced the study of Woelfer 2001 on the prevalence of PL in CUA, with the results of the meta-analysis of Venetis 2014 and Chan 2011 and updated the

	Group			The main introductory remark that "An association between congenital uterine anomalies and recurrent pregnancy loss (RPL) has been well documented", which is correct, is mainly based on two very important meta-analyses (Saravelos et al, 2008; Chan et al, 2011) examining the prevalence of CUA in the general and RPL patients and in one study (Woelfer et al, 2001) looking to the reproductive outcome of women with congenital anomalies. However, two fore coming very interesting meta-analyses (Chan et al, 2011; Venetis et al, 2014), examining the reproductive outcome of women with CUA, including all the published studies (not only Woelfer's study), are not taken into account. The main results of both support the evidence that patients with CUA have higher risk of pregnancy loss. It is obvious that if patients with CUA have higher risk of pregnancy loss, they will have higher also possibility of recurrent pregnancy loss. It might be useful to add the evidence resulting from those meta-analyses in the Guidelines.	section.
8 + 15	ESHRE/ESGE CONUTA Group			Terminology used The terminology used in the document should be useful to be consistent with the other previously published ESHRE documents. The categories of female genital anomalies in the ESHRE/ESGE classification published in 2013 (Grimbizis et al, Hum Reprod, 2013) is different than that used by the AFS (AFS, Fertil Steril, 1988). In the new ESHRE/ESGE classification uterine, cervical and vaginal anomalies are classified in independent categories giving the opportunity of a more clear description of the existing anatomical status of the anomaly. The ESHRE/ESGE uterine categories have as follows: Class 0: normal uterus, Class 1: Dysmorphic uterus (Class 1a: infantilis, Class 1b: T-shaped, Class 1c: others), Class 2: Septate uterus (Class 2a: partial, Class 2b: complete), Class 3: Bicorporeal uterus (Class 3a: partial, Class 3b: complete, Class 3c: bicorporeal septate), Class 4: Hemi-uterus or Unicorporeal uterus (Class 4a: with rudimentary cavity, Class 4b: without cavity), Class 5: Aplastic uterus (Class 5a: with rudimentary cavity, Class 5b: without cavity).	As mentioned, we used the AFS terminology for the included studies, as the studies have included the existing AFS classification. We agree that the ESHRE/ESGE classification should be used for the recommendations, and we have applied this, as suggested by the reviewer. Furthermore we added a sentence in the "additional information" section on where to find more information on the classification.

				The ESHRE/ESGE cervical categories have as follows: Class 0: normal cervix, Class 1: septate cervix, Class 2: double cervix, Class 3: unilateral cervical aplasia, Class 4: cervical aplasia. The ESHRE/ESGE vaginal categories have as follows: Class 0: normal vagina, Class 1: longitudinal non-obstructing vaginal septum, Class 2: longitudinal obstructing vaginal septum, Class 3: transverse vaginal septum, Class 4: vaginal aplasia. The exact definition of each category is clearly given in the published ESHRE/ESGE documents. Although, in the AFS classification there were not definitions but only a schematic presentation of the existing classes, there is an evident correlation between the AFS and ESHRE/ESGE classes: AFS Septate uterus: ESHRE/ESGE Septate uterus AFS Bicornuate uterus: ESHRE/ESGE Bicorporeal uterus with normal cervix AFS Didelphys uterus: ESHRE/ESGE Bicorporeal uterus with double cervix AFS Unicornuate uterus: ESHRE/ESGE {Grimbizis, 2013 #5503}. It is obvious that the existing studies had used the AFS terminology since the ESHRE/ESGE classification is new. Thus, the presentation of the existing data could follow the terminology of the AFS system. However, a note on the new ESHRE/ESGE classification could follow and the correlation between the classes of the two systems could be presented. In the recommendations the ESHRE/ESGE terminology could be used as a result of the previously provided evident correlation between the two systems' classes and the need the new ESHRE document to be consistent with the other ESHRE documents. In parentheses, the former AFS class could be presented e.g. *Metroplasty is not recommended for bicorporeal uterus with normal cervix (former AFS bicornuate uterus) and RPL* *There is insufficient evidence in favor of metroplasty in women with bicorporeal uterus and double cervix (former AFS didelphys uterus)*	
7	Michal Kunicki	65	1899	I think that it should be stressed not only serum fasting prolactin but also dynamics tests as eg> metoclopramide stimulation test (which in some centers is performed) should not be adviced	We did not include the metoclopramide stimulation test in the key questions. We have now searched for trials/studies, but we could not find any? Therefore, we

					decided not to make a comment/statement on this.
7	Michal Kunicki	63	1830	It should be added that no one general definition of IR or hyperinsulinemia exists in the literature (not only FI>20). Additionally it my opinion it should be mentioned in this paragraph that different thresholds for IR based on OGTT (60,120 min) with insulin assessment are available .	We have reformulated the sentence stating that studies have used different definitions for IR.
7	Michal Kunicki	62	1799	Thank you very much for the excellent guideline! Do not you think that despite the TPOAb are the most relevant than antibodies against thyroid gland (you cited Marai et al.2004) the recommendations should be extended on TG-antibodies screeining?	We extended the table of this paragraph with TG antibodies. However, because no association with RPL was described, we decided not to change the recdommendation
7	Mahmoud Moussa	61	1749	Is it worth it to add the value of increasing the dose of Thyroxine supplement in early pregnancy as it has been associated with better pregnancy outcome	We added text and reference to chapter 14.1: In addition, pregnancy presents a series of physiological changes which increase T4 requirements, therefore should increase their daily dose (Khan et al. Expert Rev Clin Pharmacol. 2017 Jan;10(1):97-109).
18	Recurrent Pregnancy Loss group LUMC	132	4148	Shouldn't the possible harm of (too high dose) of vitamin A also be mentioned?	We added vitamin A in the justification section
14	Recurrent Pregnancy Loss group LUMC	106	3255	The study by Johnson et al is too small to draw definitive conclusions, and do the side effects and costs of pituitary suppression and recombinant FSH also favor this treatment? Furthermore, and more importantly, this study was retracted from the BMJ in 1995 (see file)? Therefore, we advise that this recommendation should be removed	We have removed the recommendation and stated it as a conclusion.
9	Recurrent Pregnancy Loss group LUMC	83	2542	Are there intervention studies on sperm DNA fragmentation and cessation of smoking or other detrimental life style factors? As the association is only moderate, prognosis is unclear and no treatment or intervention has been studied, what is the benefit of assessing this fragmentation?	The 2 meta-analyses showing a doubling of the risk of miscarriage with sperm DNA fragmentation were just published in 2013. Thus, there has not yet been time for intervention studies to reach print. However, given the potential of this association and the absence of previous inclusion of advice for partners of women experiencing RPL, the enefit is to provide a partner risk assessment alongside the more established female profiles.

12	Recurrent Pregnancy Loss group LUMC	97	3001	From the additional information it is not clear why the guideline chooses to start before conception instead of starting as soon as pregnancy was confirmed. Could this be clarified?	We clarified the sentence, which already included antepartum administration for aspirin and heparin starting as soon as pregnant.
6	Recurrent Pregnancy Loss group LUMC	53	1441	Should patients with ANA positive sera be referred to a rheumatologist or other specialist for internal diseases because of the association with autoimmune diseases?	We don't think that patients with ANA positive sera should be referred to specialists in rheumatology or internal diseases in the absence of clinical symptoms other than RPL
6	Recurrent Pregnancy Loss group LUMC	51	1378	To state that HLA class II determination could be considered in women with secondary RPL after the birth of a boy is too early. Indeed, only one, Scandinavian study by Christiansen et al showed an effect on subsequent live birth. As haplotype frequencies of HLA vary amongst different populations, replication of this study in other ethnicities is highly important. The remark that immunotherapy could be an option is not evidence based and we advise to remove this	Although only one study has been published on the impact of HLA-DRB1 in women with secondary RPL with a firstborn boy this study was large, and there was a strong dose-response effect: patients with two "risk" HLA-DRB1 alleles exhibited a highly significantly poorer prognosis than those with "only" one risk allele" who did much worse than those with zero risk alleles. Therefore, we think that this cautious recommendation should remain. However, it could be added that the recommendation is only valid in North European populations since HLA associations are specific for ethnic groups. In the justification table, we deleted the sentence "immunotherapy could be an option"
1	Recurrent Pregnancy Loss group LUMC	26	550	We advise not to mention oocyte donation as treatment option for women with RPL, as oocyte donation itself it is associated with an increased risk for miscarriages and no experimental trials or prospective observational studies exist to underline this option.	We agree we should not have mentioned oocyte donation here, as it is not discussed in more detail in the guideline, and have delete it from the sentence
0	Recurrent Pregnanc	16	202	location).).	Corrected

	y Loss group LUMC				
0	Recurrent Pregnancy Loss group LUMC	16	198	"by the doctor and **eth** couple," > the	Corrected
A	Recurrent Pregnancy Loss group LUMC	16	200-204	In the definition of RPL also molar pregnancies and ectopic pregnancies are included? Is this patho-mechanism comparable with repeated intrauterine losses and should these pregnancies be included?	Molar and ectopic pregnancies are excluded from the definition. This was corrected.
A	Recurrent Pregnancy Loss group LUMC	15	160-163	Unclear definition. Is someone with a delivery at 22 weeks and thereafter recurrent pregnancy losses primary or secondary RPL? Suggestion: secondary RPL for previous pregnancies beyond 24 weeks	We corrected the text: secondary RPL is defined as an episode of RPL after one or more previous pregnancies progressing beyond 24 weeks' gestation
0	Recurrent Pregnancy Loss group LUMC	10	10 41	Recommendation no 41 is double with recommendation no 10	We have decided to mention this recommendation on prognosis 2 times in the guideline.
0	Recurrent Pregnancy Loss group LUMC	10 96	12.46 2983	Ante partum: consider to change to 'before conception'	Changed

O	Recurrent Pregnancy Loss group LUMC	5	135	Grammatical error; consider: Recurrent Pregnancy Loss (RPL) is defined as the loss of two or more **pregnancies**	CORRECTED
O	Recurrent Pregnancy Loss group LUMC			*We compliment the committee with finalizing this guideline. It gives a nice and complete overview of the recommendations for RPL. Thanks for all your efforts.* *Here you can find our comments, do not hesitate to contact us if there are questions.*	Thank you. Positive feedback – no action needed.
0	Giovanni Scambia Elsa Viora Nicola Colacurci			Congratulations on the excellent guidelines. Certainly this document will be very useful in clinical practice for all Italian gynecologists	Thank you. Positive feedback – no action needed.
4	Joe Leigh Simpson	Chap 4	rec 11	RCOG and many others recommend chromosomal microarray (not karyotype) for 2nd or 3rd PL. This is useful in deciding whether to treat and monitor euploid etiology like APS.	Chromosomal microarray was outside the scope of the current document. We have checked the RCOG guidance and the papers again and they do not mention chromosomal microarray, so we see no reason to modify anything.
4	Joe Leigh Simpson	Chap4	rec. 14	Should "consider" PGD for older women with a balanced translocation. Cumulative prognosis is indeed good as stated, but cumulative 71% not reported in all series and in few is pregnancy achieved in timely fashion; several reports show mean of 5 years if the patient is older (e.g., age 40) this is a problem.	Based on the study of Ikuma (2015), time to pregnancy does not differ between PGD and natural conception in RPL patients with translocation. Therefore we decided not to add this to the recommendation.
6	Joe Leigh Simpson	Chap. 6	rec. 19	Should cite work of Ober, who performed a RCT	We did not find any RCTs on HLA testing. We suggest the reviewer would like to include the RCT from Ober (1999) on Mononuclear-cell immunization, however, this study is included in the Cochrane review and meta-analysis by Wong 2014, and therefore it should not be repeated separately

8	Joe Leigh Simpson	Chap. 8	rec. 37	Skeletal anomalies (10% - 15% vertebral) are prevalent in Mulleria aplasia.	We changed this recommendation to "If a Müllerian uterine malformation is diagnosed, further investigation (including kidneys and urinary tract) should be considered."
9	Joe Leigh Simpson	Chap. 9	rec. 40	Given no treatment, it seems illogical to order DNA fragmentation outside a study.	Since there is evidence that sperm DNA damage is caused by unhealthy lifestyles (such as smoking, obesity and excessive exercise), clinicians could make couples aware of these risks. It seems reasonable to suggest a healthy alternative as a natural therapy since it is non- invasive and cost neutral.
11	Joe Leigh Simpson	Chap. 11	rec. 44	See prior comment re: potential value of PGD aneuploidy testing in older women having limited time to conceive	Based on the Ikuma study, PGD does not impact on time to pregnancy. We therefore decided not to add a comments on this.
14	Joe Leigh Simpson	Chap. 14	rec 57	Misleading as written, implying vitamin supplementation in and of itself prevents PL. Inconsistent with data reviewed. That supplementation is reasonable general advice is irrelevant for this document.	We agree that vitamin D cannot be considered an intervention to treat RPL, but is was added based on clinical expertise and questions from patients. We have revised the text and don't consider it to be misleading.
15	Joe Leigh Simpson	Chap. 15	rec. 65	Surgery for second trimester PLs for this indication should require confirmation that prior loss was euploid.	The recommendation states "PL attributable to cervical weakness" so there is , in our opinion, no need to specify that the PLs should be euploid PLs .
16	Joe Leigh Simpson	Chap. 16,	rec. 67	Misleading, implying these findings are each independently causative. Actually, each is based only on fuzzy data as stated to PL.	It is included at line 2599 that since the literature search on male factors and RPL yielded few studies the search was extended to include studies on single miscarriage. The findings are described as independently associated, but not necessarily causative.
17	Joe Leigh Simpson	Chap. 17,	Rec 74	Not just preconception but during pregnancy	We have corrected the recommendation to : Low dose folic acid is routinely started preconceptionally to prevent neural tube defects, but it has not been shown to prevent pregnancy loss in women with unexplained RPL.
0	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan			Overall, the RPL Guideline is thorough and comprehensive. However, we recommend it be shortened from 156 pages to increase the likelihood that it will be read and used as a desktop guideline in clinical practice. We also suggest that many of the recommendations need to be shortened and	We agree that the document is extensive, and we have tried to remove any unneeded data taken into account that the chapters should be stand-alone text. We will also prepare a summary version.

				more concise; if there is insufficient evidence to make a recommendation, say so.	
0	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan			As we critically reviewed the RPL Guideline, we noted that some key RPL publications were missing; we have supplied the citations for the corresponding chapters.	We have assessed each comment on missing papers and have addressed these individually
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan			The Genetics chapter needs to be expanded. We recommend a separate chapter on "Screening for genetic factors in miscarriages" and another separate chapter on "Screening for genetic factors in the RPL couple", since the etiologies and implications are quite different. With the two recent cost analyses of miscarriage chromosome testing in couples with a second miscarriage (Bernardi et al, and Foyouzi et al, Fertility and Sterility 2012), miscarriage chromosome testing is becoming the "standard of care" in most developed countries, including the United Kingdom (Royal College Green Top on Recurrent First-Trimester Miscarriage, 2011). In addition, with the theoretical, not proven, benefit of PGD-A for couples with RPL, a clear and concise section on miscarriage chromosome testing for numeric chromosome errors, and a brief section on miscarriage "copy number variants" would provide the readers with published data to make clinical decisions, and a glimpse into the future in regard to miscarriage screening.	In performing the literature study, we focused on studies in RPL, only expanding to sporadic miscarriages in the absence of any data. For this chapter, we have not assessed the studies on sporadic PL systematically, and therefore have decided not to have a separate section on this.
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan			In the chapter, "Screening for genetic factors in the RPL couple", we would suggest an additional reason to evaluate the couple for a balanced translocation would be when the miscarriage tissue is found to have a translocation (Royal College Green Top on Recurrent First-Trimester Miscarriage, 2011). When a balanced translocation is found in one of the partners, medical management and IVF/PGD should be thoroughly discussed; this section in the guideline is too brief, given the published data available. A healthcare provider with expertise in genetic and nongenetic counseling for a carrier with a balanced translocation is key.	We have added "detection of a translocation in the pregnancy tissue" as a factor in the risk analysis to prompt parental karyotyping. The comments on treatment are already discussed in the treatment chapter (chapter 11)
A	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	15	185	Would suggest not stating, "Anti-Phospholipid Syndrome, the only treatable sub-diagnosis of RPL", since this has far-reaching implications including limiting evaluation to antiphospholipid antibodies only. The RPL patient would benefit from the use of levothyroxine for overt hypothyroidism, from genetic and non-genetic counseling etc. The	This was changed to "In addition, testing for APS, a treatable sub-diagnosis of RPL, can be performed after two losses"

				International Criteria published by Miyakis et al, J thromb Haemost 2006, includes pregnancy morbidity as, "three or more unexplained (miscarriages with numeric chromosome errors excluded) consecutive pregnancy losses of less than 10 weeks size". Although this RPL guideline suggests evaluation for antiphospholipid antibodies can be considered after a couple's second pregnancy loss, this is based on association studies, not treatment studies; this should be stated.	
A	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	16	192	Suggest removing "could be considered" from the recommended definition. The Guideline Group presented evidence that supports that RPL should be defined as two or more pregnancy losses, therefore, it should be stated concisely.	This recommendation was formulated to show the discussion of the definition in the GDG. It was decided not to delete "could be considered"
A	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	definition		Would suggest also including the term, "Recurrent Miscarriage" defined as three or more consecutive pregnancy losses (Stirrat, Lancet 1990 and Royal College Green Top Guideline, as above). Therefore, "recurrent miscarriage" is a subset of "recurrent pregnancy loss".	We already defined Recurrent Miscarriage in the text (section terminology) and decided not to modify this
A	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	16	204	Would suggest REPL be defined as, "two or more pregnancy losses under 10 weeks size", as defined in the consensus statement from the ESHRE Special Interest Group Early Pregnancy (Kolte et al, Human Reproduction 2015).	We agree that both definitions should be consistent and have adapted this in the guideline.
A	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	17	221-224	Reference from Scottish registry shows prevalence of sporadic miscarriage in general population as only 5%, which, in comparison with other published studies, seems very low. On review of this manuscript, the miscarriages included are those only requiring hospital in-patient treatment. According to landmark studies cited below, the risk of miscarriage in general reproductive population is much higher; the frequency of random numeric chromosome errors decreases as the gestational age of the pregnancy at time of miscarriage increased. **Table I: Risk of Pregnancy Loss in General Reproductive Population, provided by Mary Stephenson, MD, MSc, with permission**	The prevalence of pregnancy loss was only provided as background information, but we agree that the only reference used showed low prevalence compared to other studies. We have corrected this in the document.

				<table><tr><th>Gestational Age of Pregnancy</th><th>Risk of Pregnancy Loss</th><th>Frequency of Chromosome Errors</th></tr><tr><td>< 6 weeks</td><td>30-50%[1,2]</td><td>70%[5]</td></tr><tr><td>6-10 weeks</td><td>15%[3]</td><td>50%[3]</td></tr><tr><td>>10 weeks</td><td>2-3%[4]</td><td>5%[4]</td></tr></table><u>Table References:</u> 1. Edmonds DK, Lindsay KS, Miller JF, Williamson EMB, Wood PJ. Early embryonic mortality in women. Fertil Steril 1982;38:447-453. 2. Wilcox AJ, Weinberg CR, O'Conner JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. N Engl J Med 1998;319:189-194 3. Jacobs PA, Hassold T. Chromosome abnormalities: origin and etiology in abortions and livebirths. In: Vogel F, Sperling K, eds. Human genetics. Berlin: Springer-Verlag;1987:233–244. 4. Simpson JL. Incidence and timing of pregnancy losses: relevance to evaluating safety of early prenatal diagnosis. Am J Med Genet 1990;35:165-173. 5. Ohno M, Maeda T, Matsunobu A. A cytogenetic study of spontaneous abortions with direct analysis of chorionic villi. Obstet Gynecol 1991;77:394-398.	
A	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	17	227-231	The authors state that the exact prevalence of RPL is difficult to estimate; suggest adding the publication by Roman, 1984, in which the prevalence of RPL in women trying to establish a family is 5%. This section of the chapter is quite lengthy; should be shorter and more concise. -Roman E. Fetal loss rates and their relation to pregnancy order. J Epidemiol Community Health. 1984;38:29–35 Would also suggest adding the prevalence of "Recurrent Miscarriage", quoted in the Royal College Green Top Guideline as 1-2%, based on Wyatt et al, American Journal of Obstetrics and Gynecology, 2005.	We have checked this comment. We referred to 2 recent studies (2009 and 2013) with numbers on prevalence. It is unclear whether prevalence data from 1984 are still relevant. We feel that it is more correct to state that the exact prevalence is difficult to estimate.
A	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	18	271-272	Several observational studies have demonstrated that women with RPL have high likelihood of a subsequent successful pregnancy outcome with close monitoring and supportive care. Suggest adding; • Brigham et al, Human Reproduction, 1999; cohort of women with "idiopathic recurrent miscarriage" had a 75% success rate with	After reading the study of Brigham again, we did not find a comparison between patients receiving close monitoring and those receiving standard care. Similarly, the study of Stephenson provides only indirect evidence suggesting that close monitoring is associated with high

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<td>close monitoring (n=222 pregnancies) and supportive care vs. 50% with standard prenatal care.
- Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Hum Reprod. 1999;14: 2868–2871.

• Stephenson et al, Human Reproduction, 2010, cohort of women with “idiopathic recurrent miscarriage” randomized to IVIG vs. placebo, all received close monitoring and supportive care. Both groups had equally high subsequent success rates:

Table 2: Live birth rate according to diagnosistic timing of pregnancy, provided by Mary Stephenson, MD, MSc, with permission
<table>
<tr><th>Outcome</th><th>IVIG group</th><th>Contr</th></tr>
<tr><td>Live birth rate, based on +ve hCG</td><td>70%</td><td>(</td></tr>
<tr><td>Live birth rate, excluding biochemical pregnancy losses</td><td>80%</td><td></td></tr>
<tr><td>Live birth rate once an embryo with cardiac activity was visualized</td><td>94%</td><td>9</td></tr>
</table>
-Stephenson M.D, Kutteh W.H. Intravenous immunoglobulin and idiopathic secondary recurrent miscarriage: a multicentered randomized placebo-controlled trial. Human Reproduction 2010: 25, 2203-2209.
Therefore, there is strong evidence, not “limited and weak evidence” to support that close monitoring/supportive care improves subsequent pregnancy outcomes in RPL.</td>
<td>success rate. In the absence of direct evidence on the benefit of TLC, we decided not to adapt the section as suggested.</td>
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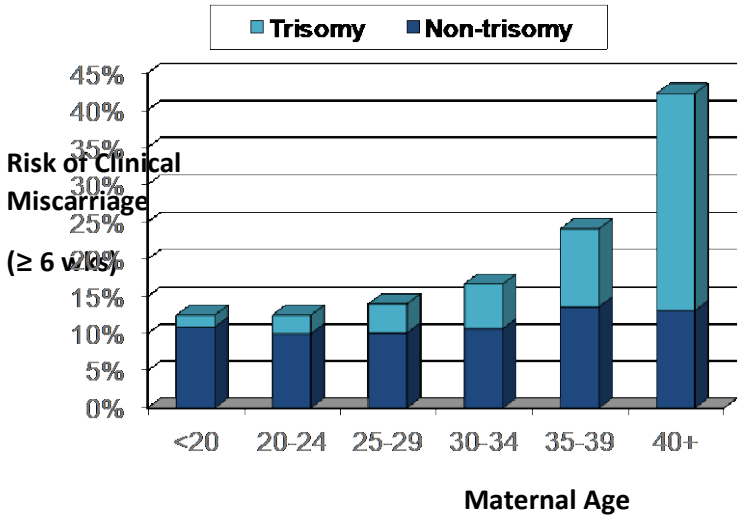
<tr>
<td>1</td>
<td>Channing Burks
Mary D. Stephenson
Theresa S. Falcon-Cullinan</td>
<td>23</td>
<td>442</td>
<td>Recommend moving “1.1 Infection” from Part C to Part D: Investigations in RPL, right before “male factors”</td>
<td>In writing the key questions, infection was classified as a risk factor, rather than a diagnostic tool. Hence, it was decided to not move the section.</td>
</tr>
<tr>
<td>1</td>
<td>Channing Burks</td>
<td>24</td>
<td>495</td>
<td>Suggest adding landmark study from Stray Pederson in regards to stress and RPL.</td>
<td>It was decided not to add this study from 1984, as it has severe limitations.</td>
</tr>
</table>

	Mary D. Stephenson Theresa S. Falcon-Cullinan			- Stray-Pedersen B, Stray-Pedersen S. Etiologic factors and subsequent reproductive performance in 195 couples with a prior history of habitual abortion. Am J Obstet Gynecol 1984;148:140–146.	
1	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	25	501	Authors have presented several studies showing that women with RPL have higher stress levels than controls and that stress is associated with RPL, however, causality is controversial. Therefore, suggest Recommendation state, "Stress is associated with RPL, but causality has not been established". Although animal studies have shown causality, further human research is needed.	To address this and other comments, we have rephrased this recommendation: Stress is associated with RPL, but patients should be informed that there is no evidence that stress is a direct cause of pregnancy loss.
1	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	25	513-519	Recommend this paragraph as applies to subfertility, fetal anomalies, stillbirth and obstetric complications, not RPL.	This is an introductory paragraph, and we moved it above the heading "evidence" to clarify this.
1	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	25	512	Suggest including a statement about advancing maternal age is associated with an increasing risk of clinical miscarriage, Hassold and Chiu study, as cited below; women over the age of 40 years old have over a 45% risk of clinical pregnancy loss at 6 weeks' vs. 15% for women under the age of 35 years. - Hassold T, Chiu D. Maternal age-specific rates of numerical chromosome abnormalities with special reference to trisomy. Hum Genet 1985;70:11-17. **Table 3: Clinical Miscarriage and Advancing Maternal Age, provided by Mary Stephenson, MD, MSc, with permission**	After assessing this suggestion, we decided that we have correctly assessed relevant evidence for the effect of age on miscarriage risk, and we don't feel adding this study from 1985 would change the recommendation.

					
1	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	26	533	Suggest removing "fetal" cytogenetic abnormalities, should only use the term "fetal" for pregnancy losses that occur at ≥10 weeks or measure >33 mm in size, according to Kolte et al. 2015. An "embryo" becomes a "fetus" at 10 wks of gestation, heralded with the formation of the bone marrow, based on Carnegie Staging.	We have rephrased the sentence
1	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	26	534	The following study by Stephenson et al. 2002, a case control study, should be included in this section as it compares frequency of euploid and noneuploid (trisomy, monosomy or polyploidy) miscarriages in couples with RPL to the general reproductive population. The study reported that women under 36 years with a history of RPL had a higher frequency of euploid miscarriage than age-matched controls. In contrast, women of at least 36 years with a history of RPL had a similar frequency of euploid miscarriage when compared to age-matched controls. As expected, with advancing maternal age, the frequency of euploid miscarriages decreased and trisomic miscarriages increased. -Stephenson MD, Awartani KA, Robinson WP. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case control study. Hum Reprod 2002;17:446-451.	This study was assessed but excluded from the evidence for the genetics chapter as the data were included in the review of van den berg 2012.

1	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	26	542	Suggest changing this Recommendation, as this statement applies to the general reproductive women, not women with RPL. As stated above, women <36 years with a history of RPL have a higher frequency of euploid miscarriages than in age-matched controls, which suggests that factors associated with RPL are more likely to be found in women <36 years. Marguard et al, Fertility and Sterility, 2010, reported that in women over 35 years with a history of RPL, numeric chromosome errors are responsible for the majority of miscarriages. -Marguard K, Westlphal 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. Therefore, based on these studies and others, would suggest the Recommendation state, "Women over 35 years with a history of RPL should be advise that the most likely cause of their miscarriages is random chromosome errors".	These data are more appropriate for the genetics chapter than for the risk factors. In this chapter. We have explored whether or not age is a risk factor for RPL, and the recommendation forms a reply to this question. We decided not to elaborate on possible reasons for the impact of age on RPL.
1	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	26	551-552	Would suggest deleting this sentence. As an aside: Disagree with making strong statements based on low quality evidence, the strength of recommendations should correlate with the quality of evidence available.	We have deleted the sentence. Regarding the strength of the recommendation (strong or weak), it depends on the quality of evidence available (indicated high-very low), but also other factors are considered, including patients perspective, balance of benefits versus harms, clinicians perspective. As such, a strong recommendation can be formulated based on moderate evidence.
2	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	32	765	Would suggest recommending zero alcohol consumption, smoking or illicit drug use in pregnancy; several studies have demonstrated adverse fetal effects and adverse pregnancy outcoes.	We agree that ideally any (pregnant) women should be recommended zero alcohol and smoking. But after careful consideration and discussion on how such recommendation could be interpreted by RPL couples, we decided to recommend smoking cessation and limiting alcohol.
3	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	35	869	Do not agree that there is enough evidence available currently to recommend/support testing HLA or sperm fragmentation in couples with RPL; suggest modifying this sentence.	We have changed this to "can be relevant only in selected RPL couples"
4	Channing Burks	37	902	Suggest changing title from "Genetic Analysis of Pregnancy Tissue" to "Miscarriage Chromosome Testing"	We decided not to change this as suggested

	Mary D. Stephenson Theresa S. Falcon-Cullinan				
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	37	910	Suggest changing "genetic abnormalities of the fetus" to "numeric chromosome errors in the miscarriage"; should only use the term "fetus" for pregnancy losses that occur at ≥10 weeks or measure >33 mm in size, according to Kolte et al, 2015. Also suggest adding to this section that trisomy, monosomy and polyploidy are the most common numeric chromosome errors found in miscarriages in women with RPL (Stephenson et al, Human Reproduction 2002) and in the general reproductive population (see Table 1 above).	We changed the term "fetus" in the sentence
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	37	922	Array CGH has not been shown to be a "better technique", it has its limitations including; • aCGH does not identify balanced translocations • aCGH does not identify polyploidy aCGH requires a reflex step, just like conventional cytogenetic analysis, with a female euploid result to determine whether it is of pregnancy or maternal origin.	We feel that we correctly termed Array CGH as the "better" technique, and we have listed the limitation of Array CGH.
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	37	927	Suggest being consistent and changing "pregnancy tissue" to "miscarriage tissue".	We had initially used the term miscarriage tissue, but it was decided to change it to "pregnancy tissue"
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	37	929	In regard to Bernardi et al, Fertility and Sterility 2012, based on modeling, the authors recommended miscarriage chromosome testing at time of 2nd miscarriage to help identify couples that warrant an RPL evaluation. If the 2nd miscarriage had a numeric chromosome error (trisomy, monosomy or polyploidy), the couple should be encouraged to try again without further RPL evaluation since their history consists of 1 "unexplained" miscarriage and 1 "explained" miscarriage due to a random chromosome error. Conversely, if the 2nd miscarriage was euploid, then the couple had 2 "unexplained" miscarriages which would justify an RPL evaluation to assess for maternal and paternal factors associated with RPL.	The last sentence for this paragraph was not well formulated and confusing. We corrected the sentence.

4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	38	939	Disagree with recommendation that the genetic analysis of pregnancy tissue is not routinely recommended. Chromosome testing of the 2nd miscarriage has been shown to be a cost savings strategy to identify which couples warrant an RPL investigation (Bernardi et al, Fertility and Sterility 2012; Foyouzi et al, Fertility and Sterility 2012). Miscarriage chromosome testing determines whether the miscarriage is "unexplained", therefore requiring further evaluation, vs. "explained" due to a random numeric chromosome error (trisomy, monosomy, polyploidy). This information is important for both the couple and the healthcare provider. McNally et al, Journal of Reproduction Medicine 2016, reported that the majority of patients experiencing first trimester miscarriage desire chromosome testing.	The main reason for not recommending routine genetic screening was that the result only provides an explanation for the miscarriage, but it does not help in providing treatment options. It was decided not to change the recommendation.
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	38	940	Studies have shown if the healthcare provider separates the miscarriage tissue from maternal decidua, as described by Lathi et al, Journal of Assisted Reproductive Genetics 2002, and in video by Lathi et al, Fertility and Sterility 2014, the frequency of maternal contamination is markedly reduced. Microsatellite analysis should be used as a reflex test if conventional cytogenetic analysis or aCGH is performed • 22% of 46,XX results were of maternal origin with conventional cytogenetic analysis. Stephenson MD, Awartani KA, Robinson WP. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case control study. Hum Reprod 2002;17:446-451. • 23% of 46,XX results were of maternal origin with aCGH. Mathur et al, Fertility and Sterility 2014;101:1349-1352.	We assessed this comment, but we feel that we have already addressed this issue in the guidelines document, with reference to the relevant papers.
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	38	960	Evaluation of recurrent miscarriage found that one of the partners was a carrier of a balanced translocation in 3.5% of couples. -Stephenson MD. Frequency of factors associated with habitual abortion in 197 couples. Fertility and Sterility 1996;66:24-29.	We report the best available evidence, and other studies are available assessing prevalence in much higher number of patients.
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	39	982	Suggest adding the van den Boogaard et al, Human Reproduction 2010. The conclusion of this study is that the sequence of preceding pregnancies is not a risk factor for carrier status. Therefore, couples with miscarriages interspersed with healthy child(ren) should be managed the same as	The study of van den Boogaard is discussed in the chapter on definition. As we do not differentiate between primary and secondary RPL, or consecutive vs non-consecutive, we have decided not to repeat the study here.

				couples with consecutive miscarriages, in other words, the pregnancy losses do not need to be consecutive.	
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	40	1009-1013	Suggest removing this paragraph as written. IVF/PGD has not been shown to improve the live birth rate, compared to medical management and close monitoring/supportive care, in couples with RPL in whom one of the partners has a balanced translocation. As written, it is encouraging IVF/PGD for such patients, which is not evidence-based. References include; -Stephenson MD, Sierra S. Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. Hum Reprod 2006;21:1076-1082. -Desjardins MK, Stephenson MD. "Information-rich" reproductive outcomes in carriers of a structural chromosomal rearrangement ascertained on the basis of recurrent pregnancy loss. Fertil Steril 2012;97:894-903 -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. Sem Reprod Med 2011;29:470-481. -Stephenson MD, Goddijn M. A critical look at the evidence does not support PGD for translocation carriers with a history of recurrent losses.	First of all, IVF/PGD is not discussed here, and we refer to chapter 11 for that. The sentence discussed the impact genetic testing may have on the decision-making of RPL couples. Therefore we decided not to change the sentence
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	41	1111	The GreenTop Guideline No. 17 from 2011 from the Royal College of Obstetricians and Gynaceologists recommends performing parental karyotyping of both partners with RPL if miscarriage chromosome testing result reveals a balanced translocation. Recommend including the RCOG Guideline and suggest adding this as a Recommendation.	We have added that a translocation detected in miscarriage tissue is a factor to be included in the risk assessment for parental karyotyping,
5	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	44	1168	Suggest adding the well-established international pregnancy history criteria for APS (Miyakis et al, Journal of Thrombosis and Haemostasis 2006), which reads, "three or more unexplained (numeric chromosome errors not included) consecutive spontaneous miscarriages before the 10th week of gestation".	We have copy-pasted the full criteria from the Miyakis paper in the sentence.
5	Channing Burks Mary D. Stephenson	44	1170	The study of van den Boogaard et al, 2013 is retrospective, comparing demographics between women with two pregnancy losses versus three pregnancy losses. Association studies do not equate to cause. Prospective	We have changed the description of the paper based on this comment.

	Theresa S. Falcon-Cullinan			studies are needed to determine whether testing for antiphospholipid antibodies is warranted after two early pregnancy losses.	
5	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	44	1171	Recommend changing to "two or more unexplained pregnancy losses", meaning that pregnancy losses with chromosome errors have been excluded.	The sentence suggested to be revised has been rewritten after adding the Myakis criteria
5	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	45	1173	Suggest adding the following reference which provides data showing that the lupus anticoagulant is the primary predictor of adverse pregnancy outcomes in women who test positive for at least one antiphospholipid antibody. -Lockshin MD, Kim M, Laskin CA, Guerra M, Branch DW, Merrill J, Petri M, Porter TF, Sammaritano L, Stephenson MD, Buyon J, and Salmon JE. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody in patients with antiphospholipid antibodies. Arthritis & Rheumatism 2012;64:2311-2318	In our literature study we focused on RPL, or miscarriage. Hence we did not include any studies focusing on adverse pregnancy outcomes.
5	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	45	1204	This recommendation is based on association studies only, none of which show causality, therefore, your conclusion is not based on strong evidence. If the Recommendation is to test for antiphospholipid antibodies after two early pregnancy losses, suggest stating after "two unexplained early pregnancy losses", since 50-70% of early (<10 wks) pregnancy losses are due to a random chromosome errors.	This recommendation is not based on strong evidence, it is based on low quality evidence, labeled ⊕⊕◯◯. Taken into account that screening can provide diagnosis, treatment, cause and prevention of complications (ie high benefit), without significant harms, the GDG decided to formulate a strong recommendation. We did not add "unexplained" to the recommendation, as unexplained RPL is generally used for RPL in which all diagnostic tests where performed and none found a positive result. Adding unexplained here would be incorrect, especially as genetic testing is not recommended for all losses.
5	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	46	1206	Suggest revision of this Recommendation, as it is based on association studies only. Although no association was noted in the 5 studies listed, these studies only looked at losses prior to 13 weeks and many couples with RPL and APS have pregnancy losses ≥10 weeks size. A deviation from the International Consensus of APS (Miyakis et al, Journal of Thrombosis and Haemostasis 2006), to not screen for B-2GP-1, should be based on outcome studies that focus on live birth rates and adverse pregnancy outcomes, not association studies alone.	The recommendation on B-2GP-1 is not evidence based, as indicated by the label GPP. We only state that this can be screened for future knowledge.

6	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	53	1441	ANA is a nonspecific autoimmune marker; the most common cause of a positive ANA is autoimmune thyroid disease, followed by other autoimmune diseases. Based on published data, there is little evidence to suggest a causal effect between positive ANA and RPL, therefore, testing should not be recommended.	A causal link between APL and TPO abs and RPL has either not been documented but in spite of this we recommend screening for these two antibodies. Proven causality is not a criterium for recommending investigation in RPL If there is a documented association and good evidence of a prognostic impact
7	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	61	1757	The study by Bernardi et al, Fertility and Sterility 2013, reported no difference in the live birth rates in women with RPL that were treated for SCH and those who were not.	The observational cohort study of Bernardi was used to discuss the prevalence of SCH and possible impact of SCH on LBR. The results of the treated versus untreated comparison have been included in the treatment chapter.
7	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	61	1769	Based on the three studies cited (Bernardi et al, 2013; van Dijk et al, 2016; Lata et al, 2013), women with RPL were found to have a higher prevalence of SCH as compared to the general reproductive population, but live birth rates in women with SCH did not significantly differ from women with RPL who were euthyroid, irrespective of whether they were treated or not for SCH.	This is the same conclusion as in the guideline, except for the sentence "irrespective of whether they were treated or not for SCH". Treatment for SCH is discussed in a separate key question in chapter 14
7	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	63	1807	This section on PCOS needs to be more concise since routine testing for PCOS is not recommended for women with RPL.	The section includes studies on PCOS and on disturbances of the insulin metabolism, and although testing for neither PCOS, nor Insulin resistance is recommended, several studies have evaluated this, and are worth mentioning.
7	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	65	1878	Suggest adding the following study to this section, as it is the only RCT that has been done in women with RPL and hyperprolactenemia. -:Hirahara F, Andoh N, Sawai K, Hirabuki T, Uemura T, Minaguchi H. Hyper- prolactinemic recurrent miscarriage and results of randomized bromocrip- tine treatment trials. Fertil Steril 1998;70:246–52.	This study has been discussed in the treatment chapter when discussing treatments for RPL in women with hyperprolactinemia. We decided not to repeat it here.
7	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	66	1899	Based on the above RCT, suggest changing the Recommendation for testing for prolactin in women with RPL since the RCT, albeit small, showed that treatment with bromocriptine improved the live birth rate. Prolactin testing is very inexpensive.	We had formulated the recommendation taken into consideration the study of Hirahara. At this point, we see no reason to reconsider the recommendation on screening.

7	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	69	1992	Stephenson et al, 1996; Badawy and Westphal, 2000; and Balasch et al, 1986, found an association with luteal phase insufficiency and RPL. Therefore, prospective studies are needed to further assess luteal phase insufficiency in women with RPL. Therefore, this Recommendation should be changed to reflect this.	As explained in the justification section, we concluded that there is inconsistent evidence of an association (based on all retrieved studies, including the 3 mentioned). Furthermore, there is no clear value for prognosis or treatment. The GDG feels that this should not be the priority of future research, and based on other comments, we added a sentence stating that "Based on the current evidence, luteal phase insufficiency should not be the focus of future trials in RPL"
7	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	72	2084	This Recommendation should be changed; "inconsistent" evidence to make a recommendation.	There is indeed inconsistent evidence for an association with LH, and for an impact on prognosis. However, the guideline group felt that recommending against routine LH testing would be appropriate (as based on current evidence, there is no benefit of testing)
8	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	79	2384	Suggest modifying this Recommendation, "All women with RPL should have an assessment of their uterine cavity". Delete stating this should be done with a pelvic ultrasound.	We changed the recommendation as suggested
8	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	79	2385	Disagree with this Recommendation. 3D US may has the highest sensitivity and specificity for certain uterine anomalies, but hysteroscopy, which allows for direct visualization of the uterine cavity is able to detect more subtle findings including retained pregnancy tissue, adhesions and polyps.	We have revised this and other comments and still believe hysteroscopy is more invasive and thus 3D US is preferable.
9	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	82	2474	Suggest "40-50% of RPL remaining unexplained, termed "idiopathic" RPL, cite Stephenson, Fertility and Sterility 1996. Delete "possible male factors have still not been satisfactorily addressed" since the evidence is insufficient to state this.	We do not state that unexplained RPL is male factor-RPL, but only that male causes are not investigated in RPL, and thus not accounted for in the numbers. We have rephrased the sentence slightly to clarify.
9	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	83	2510	Suggest not including studies which look at sperm DNA damage in couples undergoing ICSI or IVF; this does not apply to couples with RPL.	The studies included also contained miscarriages from couples after spontaneous conception. They were not significantly different from those who miscarried after ART

9	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	83	2531	Delete this paragraph; these studies do not apply to couples with RPL.	The studies included also contained miscarriages from couples after spontaneous conception. They were not significantly different from those who miscarried after ART
9	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	83	2542	Suggest deleting this Recommendation; not based on direct evidence in couples with RPL. DNA fragmentation testing is expensive, and the treatment is even more expensive and unproven in RPL!	DNA fragmentation is only around £250 per test. Further, unlike women who are offered a range of tests, here is no other test for men. See lines 2534-2571: these data are from men with miscarriage compared with successful pregnancies. It is included at line 2599 that since the literature search on male factors and RPL yielded few studies the search was extended to include studies on single miscarriage. Given the potential of this association and the absence of previous inclusion of advice for partners of women experiencing RPL, the benefit is to provide a partner risk assessment alongside the more established female profiles In terms of treatments, the recommendation is that antioxidants for men have not been shown to improve the chance of a live birth in couples with RPL.
10	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	86	2664	The study by Kolte et al 2014 concluded that non-visualized losses had the same negative impact on subsequent live birth as clinically documented miscarriages. This study did not comment on the impact of the number of previous pregnancy losses.	We have rephrased the sentence
11	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	91	2803	Suggest separate sections on IVF/PGD for RPL with a known translocation carrier, and IVF/PGD-A for women with unexplained RPL. Delete publications which do not address RPL. The study by Murugappan et al, Human Reproduction 2016, is included, but the study by Murugappan et al, Fertility and Sterility 2015, which discusses cost effectiveness of IVG/PGD-A in RPL, should also be included. - Murugappan G, Ohno MS, Lathi RB. Cost Effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained pregnancy loss. Fertil Steril 2015;103:1215-20.	We already had separate sections for PGD-A/PGS, and PGD, but we added a sentence explaining that one is for unexplained RPL, while the other is for RP with a genetic background. We also added the study of Murugappan to the evidence section.

11	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	91	2827	Suggest adding the following discussion to this section on IVF/PGD-A for couples with RPL and a known chromosomal rearrangement. Stephenson MD, Sierra S. Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. Hum Reprod 2006;21:1076-1082. -Desjardins MK, Stephenson MD. "Information-rich" reproductive outcomes in carriers of a structural chromosomal rearrangement ascertained on the basis of recurrent pregnancy loss. Fertil Steril 2012;97:894-903 - 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. Sem Reprod Med 2011;29:470-481. -Stephenson MD, Goddijn M. A critical look at the evidence does not support PGD for translocation carriers with a history of recurrent losses.	The study of Stephenson 2006 was listed in the discussion in chapter 4, but not in chapter 10, as it is included in the review of Franssen 2011. The review of Hirshfeld-Cytron was judged as insufficient quality and the last reference was a letter to the editor. Therefore none of these papers were listed in the guideline
12	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	96	2960	There is evidence that LMWH is as efficacious to UFH; Stephenson et al, 2004, published a RCT which reported similar pregnancy outcomes when comparing dalteparin (LMWH) to unfractionated heparin, both in combination with low dose aspirin for treating APS. -Stephenson MD, Ballem PG, Tsang P, Purkiss S, Ensworth S, Houlihan E, Ensom MH. Treatment of antiphospholipid antibody syndrome (APS) in pregnancy: a randomized pilot trial comparing low molecular weight heparin to unfractionated heparin. Journal of Obstetrics and Gynaecology Canada 2004;26:729-734.	The study mentioned was included in the literature overview of Bates 2012. However, overall, systematic reviews did not report a significant benefit for LMWH.
12	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	96	2983	Suggest changing this Recommendation to three or more pregnancy losses, since the evidence is insufficient to support two or more, as discussed above. When to start heparin is still controversial; UFH and aspirin with positive pregnancy test, need evidence to support this recommendation.	We have changed the recommendation to 3 or more PLs, consistent with the justification section. The information on when to start treatment was based on how it was performed in the studies (not Evidence-based) but from clinical expertise it was found important to add this information to the recommendation.
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	101	3109	Suggest changing title of this section to overt hypothyroidism. Suggest changing this line to read, "Women with overt hypothyroidism should be treated with levothyroxine".	We have changed this throughout the guideline

14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	101	3114	Suggest including the 2017 Guidelines from the American Thyroid Association which recommend not treating women unless TSH >4.0.	We added the recommendations from the AT guidelines basing treatment on TSH levels and TPO-Ab status. The limit of 4.0mU/L is recommended if trimester-specific ranges are not available
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	101	3118 3136-3139	Suggest removing the studies that evaluated anti-TPO antibodies in women without a history RPL, i.e. Negro et al, 2010.	We did not include these studies, but only state that the recommendations of Lazarus and colleagues are based on these studies.
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	101	3124	Suggest stating that there is only one study to date that reported on women with RPL and SCH.	We added that there is only 1 study on levothyroxine treatment in RPL and SCH.
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	102	3145	This study by Lata et al. 2014 compares women with a history of RPL who are positive for +Anti-TPO antibodies to healthy controls without a history of RPL; both were groups treated with levothyroxine, no differences in miscarriage or other obstetric outcomes were noted. This study was retrospective, was not randomized, most importantly did not compare women with RPL who are positive for Anti-TPO antibodies to women with RPL who are negative for Anti-TPO antibodies. Therefore, this study does not support or refute treatment for Anti-TPO antibodies in women with RPL.	We agree that the study of Lata 2014 is an observational study reporting on pregnancy outcomes in women with TPOAB+ after LT4 treatment, rather than comparing outcomes in women with and without treatment. However, as this is the only study in RPL, we have mentioned it. We clarified the description of the study in the guideline
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	102	3151	Based on the observational study of Bernardi et al, Fertility and Sterility 2013, the evidence does not support the treatment of SCH in women with RPL. Therefore, The Recommendation should be revised.	The GDG feels that the study of Bernardi (rated very low quality) is too poor. Furthermore it contradicts evidence of benefit in non-RPL patients. We decided to keep the recommendation as formulated
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	102	3152 and 3153	Place a period after 7-9 weeks AD. Also recommend changing “eventual hypothyroidism” to “overt hypothyroidism.”	We deleted “eventual” from the sentence
14	Channing Burks Mary D. Stephenson	103	3169	Suggest moving studies by Coomarasamy et al, 2015 and Stephenson et al, 2017 to the Unexplained RPL section; the objective of both studies was to determine whether vaginal micronized progesterone improved pregnancy	Coomarasamy et al, 2015 is mentioned in the unexplained RPL section. We have revised the study of Stephenson

	Theresa S. Falcon-Cullinan			outcomes in women with unexplained RPL. Neither study defined the cohort as having “luteal phase deficiency”.	and discussed this with the group. As the patients were selected for treatment based on abnormal elevation of nCyclinE in the luteal phase, we feel it is appropriately mentioned here, even though the authors did not classify it as having “luteal phase deficiency”.
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	103	3179	Recommend adding that in the Coomarasamy study, that women were randomized to vaginal micronized progesterone “from a time soon after a positive urinary pregnancy test (and no later than 6 weeks of gestation).”	These details were added in chapter 17, but not repeated here.
14	Channing Burks Mary D. Stephenson Theresa S. Falc217on-Cullinan	103	3187	For Stephenson et al, 2017; there was an increased live birth rate in women with idiopathic RPL who were prescribed luteal start vaginal micronized progesterone compared to those who were not, 68% vs. 51% OR 2.1 (95%CI 1.0-4.4). Prospective studies are needed to confirm this finding.	We decided not to add these data from the study as the unexplained RPL patients received treatment based on their choice rather than randomization,.
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	104	3193	Suggest changing the Recommendation to state that evidence does not support the use of vaginal progesterone to improve live birth rates when started at time of positive pregnancy test and up to 6 weeks of gestation. Also suggest including a separate Recommendation that there is preliminary evidence to support the use of luteal start vaginal micronized progesterone in women with RPL.	The GDG does not agree with adding a recommendation based on the Stephenson study only
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	104	3195	Suggest removing this paragraph; the primary outcome was whether luteal start vaginal micronized progesterone improved the live birth rate in women with RPL, as stated above.	We have removed the details on the study from the justification section
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	105	3224	Suggest changing this Recommendation to, “Currently, there is no evidence upon which to make a recommendation as no studies have been done on women with RPL and PCOS”.	We have revised this comment, and decided not to change the recommendation
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	105	3248	Suggest new paragraph for the publication by Johnson and Pearce, 1990, otherwise difficult to differentiate between this publication and the one by Clifford et al, 1996.	Corrected

14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	106	3263-3265	Delete this paragraph; Recommend testing and treating hyperprolactinemia in RPL.	We moved this sentence up, outside the "evidence" section
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	107	3309	Change "harms" to "harm."	Corrected
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	107	3311	Suggest adding the ACOG recommendation, which states that women who are trying to conceive or pregnant should not use more than 2000 IU daily of Vitamin D3.	We added the information of the ACOG with regard to safety of vitamin D supplementation
14	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	108	3314	Previously stated there is inconsistent evidence of association of hyperhomocysteine and RPL, therefore, routine testing was not recommended. Based on this, should not discuss or make a recommendation in regards to treatment of hyperhomocysteinemia.	We stated that testing should be considered if clinical suspicion, so we decided to have a treatment section on this as well
15	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	112	3474	Suggest changing the Recommendation to, "There is insufficient evidence to support metroplasty". RCT needed.	We deleted the sentence on "arcuate uterus" based on a comment of another reviewer stating that "arcuate uterus" is not included anymore as a category in the ESHRE/ESGE classification, and now classified as "a septate uterus with normal function", and probably misdiagnosed in most older studies
15	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	112	3475, 3476 and 3477	Where is the evidence of association between biornuate, unicornuate and/or didelphic uterus and RPL? If no evidence of association, suggest deleting the Recommendations.	We describe an association of RPL with congenital anomalies and recommend assessment of the uterine cavity. We agree that for some of the finding from this assessment, an association with RPL is not found or investigated. However, from clinical perspective, the question on whether or not to treat these findings is relevant and therefore included in the guideline.
15	Channing Burks Mary D. Stephenson	113	3478	Discussion about arcuate is missing. Suggest making Recommendation, "There is insufficient evidence to make recommendation about arcuate uterus in RPL".	We deleted the sentence on "arcuate uterus", and also decided not to make a recommendation.

	Theresa S. Falcon-Cullinan				
15	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	113	3497	Is this recommendation based on published data, is so, include the citation(s)? If not, state the recommendation is based on consensus from GDG.	This is not a recommendation for surrogacy, but only additional information on how to approach women with irreparable CUAs.
15	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	113	3531	Suggest revising the Recommendation, "Evidence to date does not support hysteroscopic removal of submucosal fibroids or endometrial polyps in RPL".	We decided not to change this recommendation as suggested
15	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	114	3532	Suggest changing the Recommendation to, "There is insufficient evidence to recommend removing intramural fibroids which distort the uterine cavity in RPL".	We decided not to rewrite the recommendation as suggested
15	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	115	3548	Suggest changing gthe Recommendation to, "There is insufficient evidence to recommend surgical removal of intrauterine adhesions in RPL".	We decided not to rewrite the recommendation as suggested. We decided to keep the sentence on prevention of recurrence of adhesions
15	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	115	3556	Recommend authors change this section title to "Cervical Insufficiency"	Changed as suggested
16	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	119	3696-3699	Suggest removing this paragraph since studies not done on RPL cohort.	In the introduction, we state that there is moderate evidence of associations between sperm DNA quality and miscarriage. The chapter lists interventions that could reduce sperm DNA damage and miscarriage. We decided to keep the paragraph on obesity
16	Channing Burks Mary D. Stephenson	119	3706-3714:	Variocele is related to male infertility not RPL. Therefore, suggest deleting this paragraph.	Current literature suggests that surgical intervention for varicocele improves sperm DNA quality but this improvement does not translate to a reduction in miscarriages (Cho et al., 2016, Pathak et al., 2016). As the

	Theresa S. Falcon-Cullinan				repair of varicocele did not lead to a reduction in miscarriage we felt this was an important piece of information to include. However, we reduced the length of the paragraph on this.
16	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	120	3730-3736	Suggest removing this paragraph since the studies did not involve RPL.	Similar to obesity and varicocele repair, we included a section on nutrition and antioxidants. We decided to keep it.
16	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	120	3737	Suggest deleting this Recommendation since no evidence was provided in RPL.	We agree that there is no evidence in RPL, but still feel that it is clinically relevant to formulate a recommendation on lifestyle as a GPP
16	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	120	3738-3739	Suggest deleting these Recommendations since no evidence was provided in RPL.	We agree that there is no evidence in RPL, but still feel that it is clinically relevant to recommended against these options.
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	122	3795-3802	Suggest including the landmark study on LIT by Carole Ober et al, Lancet 1999. This study concluded that immunization with paternal mononuclear cells did not improve pregnancy outcome in women with idiopathic recurrent miscarriage and that this treatment caused harm. Ober et al. Mononuclear-cell immunization in prevention of recurrent miscarriages: a randomized trial. Lancet, 1999:354;365-369.	The study of Ober 1999 was included in the Cochrane review and meta-analysis by Wong 2014, and therefore it should not be repeated separately
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	122	3816	Suggest changing Recommendation to, “Based on current evidence, LIT does not improve live birth rate in idiopathic RPL and it has serious adverse effects”.	We have revised the suggested rephrasing, but decided to stick with the recommendation.
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	122	3818	Suggest removing the following sentence: “LIT should not be used in clinical practice since its scientific foundation is weak”. LIT should not be used because the evidence does not support it.	The evidence on LIT, although summarized in a Cochrane review, is based on low quality studies. As a result there is some uncertainty on the effect of LIT, and it was decided not to change the statement.

17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	123	3827	Suggest adding the study by Stephenson et al, 2010, a RCT for idiopathic secondary RPL. -Stephenson M.D, Kutteh W.H. Intravenous immunoglobulin and idiopathic secondary recurrent miscarriage: a multicentered randomized placebo-controlled trial. Human Reproduction 2010: 25, 2203-2209.	The study of Stephenson 2010 was included in the review and meta-analysis by Egerup 2015, and therefore it should not be repeated separately
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	124	3844	Recommend changing Recommendation to, "Based on current evidence, IVIG does not improve the live birth rate in idiopathic RPL".	All recommendations are based on current evidence, so it was decided not to add this to all recommendations. Specifically for this recommendation, the GDG does not believe that future evidence will change the recommendation for primary RPL.
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	124	3871	Recommend changing Recommendation to, "Based on current evidence, glucocorticoids does not improve the live birth rate in idiopathic RPL".	All recommendations are based on current evidence, so it was decided not to add this to all recommendations.
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	124	3895	Recommend changing Recommendation to, "Based on current evidence, heparin or LDA does not improve the live birth rate in idiopathic RPL".	All recommendations are based on current evidence, so it was decided not to add this to all recommendations. Based on another comment, we rephrased the recommendation to : "Heparin or low dose aspirin are not recommended, as there is evidence that they do not improve live birth rate in women with unexplained RPL"
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	125	3914	Recommend changing Recommendation to, "Based on current evidence, folic acid does not improve the live birth rate in idiopathic RPL".	All recommendations are based on current evidence, so it was decided not to add this to all recommendations.
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	126	3939	Recommend changing the wording of this sentence to, "from a time soon after positive urinary pregnancy test (up until 6 weeks) up through 12 weeks of gestation."	We adapted the sentence as suggested
17	Channing Burks Mary D. Stephenson	126		Suggest adding a sentence about luteal start vaginal micronized progesterone, based on the study by Stephenson et al, Fertility and Sterility 2017, as discussed above.	The GDG decided that, based on current evidence, there is no need to add anything about vaginal start progesterone

	Theresa S. Falcon-Cullinan				
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	126	3949	Suggest changing Recommendation to, “Based on current evidence, vaginal progesterone started after positive test does not improve the live birth rate in idiopathic RPL”.	It was decided that the study of Stephenson 2017 was not of sufficient size and quality to allow for a modification of the recommendation as suggested
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	126		Suggest adding a Recommendation, “Based on a recent observational study, luteal start vaginal micronized progesterone may improve the live birth rate in idiopathic RPL”.	We have decided not to formulate a recommendation based on this study as the results in unexplained RPL are not strong enough
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	127	3973	Recommend stating there is an ongoing trial in Egypt assessing intralipid infusion for idiopathic RPL. Remove the criticism about the trial.	We agree to delete the criticism on an ongoing trial, and have decided to delete the entire sentence.
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	127	3978	Suggest changing the Recommendation to, “Based on current evidence, intralipid therapy has not been shown to increase the live birth rate in idiopathic RPL”.	We have changed this recommendation to : “There is insufficient evidence to recommend intralipid therapy for improving live birth rate in women with unexplained RPL”
17	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	128	4018	Suggest removing this section there are no published studies in RPL.	As mentioned, the non-evidence based use of endometrial scratching is a hot topic. By including the section, the GDG states clearly that there is no evidence in RPL, and hence endometrial scratching should not be used.
18	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	132	4143	This Recommendation is unclear, suggest revision.	We have rephrased the recommendation
0 An	Channing Burks Mary D. Stephenson	143		Table 13: change title to, “Progesterone started after positive test compared to no treatment/placebo for unexplained RPL”.	The study by Stephenson 2017 was included in the chapter on treatment for endocrinologic abnormalities in RPL, but not in the chapter on unexplained RPL. The study is not a RCT and is not focused on unexplained RPL, hence

	Theresa S. Falcon-Cullinan			Suggest having a separate Table, "Progesterone started in the luteal phase compared to no treatment/placebo for unexplained RPL"; include study by Stephenson et al, Fertility and Sterility 2017.	it does not need to be added to the GRADE Table 13.
4	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	146		Suggest adding miscarriage chromosome testing in the Genetics section	We assume that the reviewer suggests to add a research recommendation on this. However, we already recommend "The role of genetic analysis of pregnancy tissue needs to be clarified" and decided not to expand on this.
0	Henriette Svarre Nielsen	6	129	First show define GDG	We have corrected this by adding "(GDG)" and we have consistently used "GDG" throughout the document"
0 An	Channing Burks Mary D. Stephenson Theresa S. Falcon-Cullinan	147		Suggest adding we need an RCT of luteal start vaginal micronized progesterone; this could be added to the female factor section.	We added a sentence on this in section 17.6
0	Henriette Svarre Nielsen	7	152	Need to have strength, quality of evidence, values and preferences and remarks	This is a conclusion rather than a recommendation. We added this to the table as a remark
0	Henriette Svarre Nielsen	7	Risk factors	Below is used patients, women and couples - it seems random.	We have changed "patients" to couples with RPL and we have checked the remaining text for consistency
4	Henriette Svarre Nielsen	8	Rec 14	Is 71% chance good in ESHRE perspective?? We aim to increase live birth and we aim for solutions to the 15-30% having troubles in getting a child. 71% is lower than the expected chance of a live birth. Leaving 29% without a child after 2 years.	This recommendation on prognosis was added to the text
5	Henriette Svarre Nielsen	8	Rec 15	This is very good formulated. Should be used other places as well	Positive feedback No action needed
0	Henriette Svarre Nielsen	8	Rec 16	Not clear. The argument is that APA may be causal and anticoagualtion can reduce pregnancy complications	We have rephrased the sentence.
6	Henriette Svarre Nielsen	9	Rec 18	Clinicians could consider offering HLA-DRB1 typing to selected patients for prognostic purpose and for deeper phenotyping but the testing will provide no change in treatment offers.	We have decided not to add "for deeper phenotyping" as this is not discussed as a reason for testing in the chapter

6	Henriette Svarre Nielsen	9	Rec 20	technical challenges?	Technical challenges with Cytokine testing are related to measurement in endometrial or decidual tissue or endometrial flushings This is explained in the section 6.3, but not repeated in the summary.
0	Henriette Svarre Nielsen	9		remove "is probably"	This was corrected to be consistent with the recommendation on ANA.
0	Henriette Svarre Nielsen	11	Rec 40-79	The language is inconsistent and parts are repreated. If this list are treatments with fokus to increase live birth - it needs to be stated if the treatment can or can not be recommended.	The recommendations are formulated to reflect the opinion of the GDG; some interventions should not be used, others are not recommended, for others evidence is to limited to recommend them. All of these are not recommended, but at different levels.
14	Henriette Svarre Nielsen	11	Rec 47	remove if identified.	We corrected this. I agree this can be removed
0	Henriette Svarre Nielsen	12	Rec 52	Is the recommendation based on no impact, insufficient or limited evidence?	There is not sufficient evidence showing benefit of treatment with progesterone. This was added to the table.
0	Henriette Svarre Nielsen	12	Rec 55	This statement does not seem aligned with the recommendation	We have added that the intervention is not recommended in women with RPL, but without PCOS.
0	Henriette Svarre Nielsen	13	Rec 58	This is a good comment. Could be used other places	Positive feedback No action needed
16	Henriette Svarre Nielsen	14	Rec 69	change chance to risk in the following: but it did not significantly decrease the chance of a pregnancy loss	We corrected the sentence as suggested
17	Henriette Svarre Nielsen	14	Rec 70	Inonsistent language compared to rest of recommendations: LIT are not recommended as a treatment of...	For this intervention the GDG decided to state that it should not be used, which is stronger than stating “it is not recommended”.
17	Henriette Svarre Nielsen	14	Rec 71	Remove for the time being. As the whole guideline is build on for the time being.	We changed this to “based on the available evidence”

17	Henriette Svarre Nielsen	14	Rec 73	Heparin or low dose aspirin are not recommended as a treatment for unexplained RPL	We have rephrased the recommendations.
17	Henriette Svarre Nielsen	14	Rec 75	Vaginal progesterone is not recommended as a treatment of unexplained RPL	We decided not to reformulate the recommendation as suggested
17	Henriette Svarre Nielsen	14	Rec 76	Intralipid therapy is not recommended as treatment of unexplained RPL	For this intervention the GDG decided to state that it should not be used, which is stronger than stating "it is not recommended".
17	Henriette Svarre Nielsen	15	Rec 78	Endometrial scratching is not recommended as a treatment of unexplained RPL	For this intervention the GDG decided to state that there are no studies on this.
17	Henriette Svarre Nielsen	14	Rec 77	G-CSF is not recommended as a treatment of unexplained RPL	For this intervention the GDG decided to state that there is insufficient evidence for a recommendation, rather than recommending against the intervention.
A	Henriette Svarre Nielsen	16	159	and different definitions apply in different countries several countries (Nordic) using GA 22.	We added this sentence to the guideline
A	Henriette Svarre Nielsen	16	163	This definition is not complete. Patients with PL after a pregnany reaching 20-24 is not categorised. Secondory RPL is a series of losses after a previous birth independent of it being a live or stillbirth.	This was corrected
A	Henriette Svarre Nielsen	16	174	Carrier status needs to be defined	This was corrected
0	Henriette Svarre Nielsen	16	183	Somewhere guideline group is abbreviated GDG others places not..	We corrected this
A	Henriette Svarre Nielsen	18	220-224	This is low compared to the 1: Nybo Andersen et al. Maternal age and fetal loss: population based register linkage study. BMJ. 2000;320(7251):1708-12. 2: Wilcox et al. Incidence of early loss of pregnancy. N Engl J Med. 1988;319(4):189-94.	We revised this section and added the study of Nybo Andersen
A	Henriette Svarre Nielsen	18	251	Pregnancy loss	Corrected

B	Henriette Svarre Nielsen	21	373	perhaps mention information meetings. There are RPL units (Danish RPL unit) where information meetings for refereed patients are hold 4 times a year. 2 hours including history of prior patient	A sentence on information sessions was added to the section.
B	Henriette Svarre Nielsen	22	380	Maybe risk factor is more appropriate than cause	In this sentence "cause" may be better, as patients would have questions on what has caused their previous loss(es)
1	Henriette Svarre Nielsen	25	483	lack of micronutrients	Corrected
1	Henriette Svarre Nielsen	26	505	Poor evidence or lack of evidence can not be used to reassure	We have changed the sentence; patients can be informed that there is no evidence for a causal association.
1	Henriette Svarre Nielsen	26	529	Larger study: Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. BMJ. 2000; 320(7251):1708-12.	We added the reference to section 1.4
1	Henriette Svarre Nielsen	27	546	Female age is shown to be of importance in almost all studies on outcome in RPL. Studies on miscarriage risk with age are based on full national data and can therefore not be considered of low quality	According to the GRADE system (with known limitations for non-intervention studies), observational studies are "low" quality, which is why the recommendations are graded ⊕⊕◯◯. This does not judge the quality of the individual studies
2	Henriette Svarre Nielsen	30	649	From the mentioned study it seems that smoking is a significant risk factor. But whether cessation reduces the risk is unexplored	We mentioned no studies in RPL that show smoking is a risk factor; the study of Zhang concluded that "female smoking" is not associated with RPL. Therefore we believe "Smoking has not been conclusively shown to be a risk factor for RPL" is correct
2	Henriette Svarre Nielsen	30	676	Association between euploid losses and high BMI is also shown in this study on sporadic miscarriages: Landres IV, Milki AA, Lathi RB. Karyotype of miscarriages in relation to maternal weight. Hum Reprod. 2010 May;25(5):1123-6.	We have only added data in sporadic PL in sections where there is insufficient evidence in RPL, which is why this reference is not included.
2	Henriette Svarre Nielsen	31	702	Based on above studies there is an association between obesity and PL and euploid losses. No evidence that weight reduction decreases risk of PL	We have reviewed this comment and feel the recommendation correctly reflect that there is an association between obesity and pregnancy loss in women with RPL.

2	Henriette Svarre Nielsen	32	734	There is this review: Hegaard HK, Ersbøll AS, Damm P. Exercise in Pregnancy: First Trimester Risks. Clin Obstet Gynecol. 2016 Sep;59(3):559-67. Looking at risk of PL (not RPL) and Excercise.	We added the conclusion of the Hegaard review to the guideline
2	Henriette Svarre Nielsen	33	765	Based on data from PL ...	The recommendation already stated that alcohol is a possible risk factor for PL (not RPL). We did not add "based on data from PL"
2	Henriette Svarre Nielsen	33	773	lack of or poor evidence can not be used to reassure.	We have changed the recommendation reflecting that patients should be informed, rather than reassured based on poor evidence
2	Henriette Svarre Nielsen	33	787	Of	Corrected
3	Henriette Svarre Nielsen	36	875	Is the 2,2% low? The frequency of parental carriers of balanced chromosmal abnormalities. The largest referred behow found 1,9% of couples referred for genetic testing. But higher frequency has been reported from smaller studies.: Some have reported a frequency of 5% of RPL couples: 1: Ocak Z, Özlü T, Ozyurt O. Association of recurrent pregnancy loss with chromosomal abnormalities and hereditary thrombophilias. Afr Health Sci. 2013 Jun;13(2):447-52. doi: 10.4314/ahs.v13i2.35. PubMed PMID: 24235948; PubMed Central PMCID: PMC3824507. 2: Kochhar PK, Ghosh P. Reproductive outcome of couples with recurrent miscarriage and balanced chromosomal abnormalities. J Obstet Gynaecol Res. 2013 Jan;39(1):113-20. doi: 10.1111/j.1447-0756.2012.01905.x. Epub 2012 Jun 4. PubMed PMID: 22672580.	We have assessed both papers and excluded them as we focused on larger studies in a European context.
4	Henriette Svarre Nielsen	39	945	This study shows a correlation between aneuploidy and number of pL: Ogasawara et al. Embryonic karyotype of abortuses in relation to the number of previous miscarriages. Fertil Steril. 2000;73(2):300-4	The study of Ogasawara 2000 was excluded as the data were included in the review of Van den Berg 2012.
4	Henriette Svarre Nielsen	40	964	This is inconsistent with the statement above and below that the cumulative rate is >71 %	The success rate was 64% in the study of Flynn 2014, we moved the reference to clarify this.
4	Henriette Svarre Nielsen	41	1008	Again this is strange given the largest study not restricted to patients age above 39 found 1,9% carriers	The Barber cohort study indeed reported a balanced chromosome abnormality in 1.9% of 20432 RPL patients. The Franssen case-control study looked at factors

					influencing the probability of carrier status and concluded that for some couples, the probability of carrier status is so low, that it can be considered not testing these couples. We deleted "(below 2.2%)" in this sentence, as it can be confusing, and is irrelevant as the Franssen study was not designed to study prevalence.
6	Henriette Svarre Nielsen	51	1350	Incorrect the prognostic impact of HY-restricting HLA-Class I is investigated as described above - and below. Suggest chaning this sentense	We have revised the entire section on HY-antibodies and added a sentence on the prognostic impact
6	Henriette Svarre Nielsen	51	1355	or zero	This was corrected
6	Henriette Svarre Nielsen	52	1380	Suggest: Immunotherapy should be tested according to HLA status.	We have added this as a research recommendation.
6	Henriette Svarre Nielsen	57	1522	The prospective impact is studied here: Nielsen HS, Witvliet MD, Steffensen R, Haasnoot GW, GoulmyE, Christiansen OB, Claas F: The presence of HLA-anti bodies in recurrent miscarriage patients is associated with a reduced chance of a live birth. J Reprod Immunol 2010; 87:67–73 The high frequency of HLA abs in unexplaned secondary RPL with a firstborn boy indicate that further phenotyping of patients is needed	We added a sentence on the prognostic impact of HLA-AB based on the study of Nielsen 2010
6	Henriette Svarre Nielsen	57	1523	The two studies did almost show significant heterogeneity.	We have checked the meta-analysis and find that our statement "but the included studies showed significant heterogeneity" is correct
7	Henriette Svarre Nielsen	71	2048	There is one (however published after guideline) meta-analysis showing very low level of Vit D as a risk factor. Another study showing an associaiton between VIt D and PL: Zhang H, Huang Z, Xiao L, Jiang X, Chen D, Wei Y. Meta-analysis of the effect of the maternal vitamin D level on the risk of spontaneous pregnancy loss. Int J Gynaecol Obstet. 2017 Sep;138(3):242-249. doi: 10.1002/ijgo.12209. Epub 2017 Jun 19. Review. PubMed PMID: 28500757. 2: Hou W, Yan XT, Bai CM, Zhang XW, Hui LY, Yu XW. Decreased serum vitamin D levels in early spontaneous pregnancy loss. Eur J Clin Nutr. 2016 Sep;70(9):1004-8. doi: 10.1038/ejcn.2016.83. Epub 2016 May 25. PubMed PMID: 27222154; PubMed Central PMCID: PMC5023787.	We found some studies of vit D in RPL, so we did not expand the search to spontaneous PL. Therefore we did not include the papers. In addition, the study of Zhang was published after the inclusion deadline (March 2017)

7	Henriette Svarre Nielsen	72	2077	Of	Corrected
9	Henriette Svarre Nielsen	84	2520	Coherent?	Corrected
/	Miscarriage Association	/	/	I found it interesting and I was pleased they also recognized the psychological impact of miscarriage on both parents. It recognizes the importance of specialist clinics staffed by appropriately trained individuals forming a multidisciplinary team to support patients in a suitable environment. It recognizes that there are limited tests of any true value and that treatment may not be available in the majority of cases. Lifestyle factors could be emphasized further with clearer guidance on alcohol and drugs. I have met many patients who drink a bottle of wine a night or who use cannabis or cocaine. The guideline has reviewed the current evidence available for investigations and treatments and has provided a platform to build upon with a broad range of recommendations for future research. It also dismisses some of the more unusual treatment practices such as immuno-therapy, intralipid therapy, IVF etc which is only available privately and some of which are viewed as unsafe. This is group of vulnerable patients who are often willing to try anything to achieve a baby so this information is crucial.	Thank you for the feedback. We will stress these points in the patient leaflet.