Recurrent pregnancy loss

Dr. Mahmoudinia
,Mashhad university of Medical science

Definition

- Three or more consecutive spontaneous miscarriages. (not necessarily consecutive) before 20 weeks of gestation
- Recurrent pregnancy loss (RPL) is defined as the loss of **two or more** pregnancies **until 24 weeks of gestation**
- Two or more failed clinical pregnancies as documented by ultrasonography or histopathologic examination or Three consecutive pregnancy losses, which are not required to be intrauterine

TABLE 2 COMPARISON OF THE ELEMENTS OF RPL DEFINITIONS IN THREE (INTER)NATIONAL GUIDELINES

	ESHRE2017	ASRM2013	RCOG2011
Pregnancy	Serum or urine HCG; ectopic and molar pregnancies not to be included in the definition	Clinical pregnancy documented by ultrasonography or histopathological examination	All pregnancy losses not further defined
Weeks of gestation	Up to 24 weeks	Only mentions that majority is lost prior to 10th week	Up to 24 weeks
Recurrence	2	2	3
Consecutive	Consecutive or non-consecutive	Consecutive	Consecutive

ASRM = American Society for Reproductive Medicine; ESHRE = European Society of Human Reproduction and Embryology; HCG = human chorionic gonadotrophin; RCOG = Royal College of Obstetricians and Gynaecologists; RPL = recurrent pregnancy loss.

When do we start investigating ?

UP TO DATE

three or more consecutive spontaneous miscarriages consecutive

we start investigating after two failed clinical pregnancies, including biochemical pregnancies for women undergoing in vitro fertilization

- Two consecutive spontaneous miscarriages with one of :
- Embryonic heart activity observed before any earlier pregnancy loss.
- Normal karyotype on products of conception from an earlier loss.
- Female partner age over 35 years.
- Infertility

Couples with recurrent pregnancy loss (RPL) require empathy and understanding as early pregnancy loss is an emotionally traumatic experience, similar to that associated with stillbirth or neonatal death.

In addition, evaluation can be frustrating and difficult because the etiology of their RPL may not be determined and there are few evidence-based diagnostic and treatment strategies.

- There should be individual evaluation of the investigations appropriate to each woman or couple, based on age, fertility/sub-fertility, pregnancy history, family history, previous investigations and/or treatments. In addition, care should be tailored to the psychological needs of the couples

Causes of RPL

- Genetic
- Anatomic,
- Immunologic
- Endocrine
- Thrombophilic
- Infectious

Investigations

lifestyle,

Genetic analysis

Thrombophilia

Metabolic tes

Uterine anatomy

Male factor

Immunologic

Risk factors and health behavior modifications

- Previous pregnancy losses
- Age
- smokers
- Alcohol
- Caffeine
- Medication, antiprogestogens, antineoplastic agents, and
- inhalation anesthetics, exposure to ionizing radiation, prolonged exposure to organic solvents, and exposure to environmental toxins, especially bisphenol-A and heavy metals

- obesity or being significantly underweight
- Stress

Genetic factors

- 50% of all first-trimester pregnancy losses, 30% of second-trimester abortuses, and 3% of stillbirths are chromosomally abnormal
- Numerical (aneuploidy, polyploidy)
- Structural abnormalities (translocations, inversions)
- Autosomal trisomy are the most common abnormality (usually involving chromosomes 13–16, 21, or 22), followed by monosomy X (45,X) and polyploidies

What is the value of screening for genetic factors in the diagnosis of RPL?

- Genetic analysis of pregnancy tissue
- Parental karyotyping

Genetic techniques

- Conventional karyotyping
- Fluorescence *in situ* hybridization [FISH]
- Array–based comparative genomic hybridization [array-CGH])
- Next generation sequencing (NGS)

Anatomical factor

- Congenital uterine malformations

Class I segmental,mullerian agenesis-hypoplasia

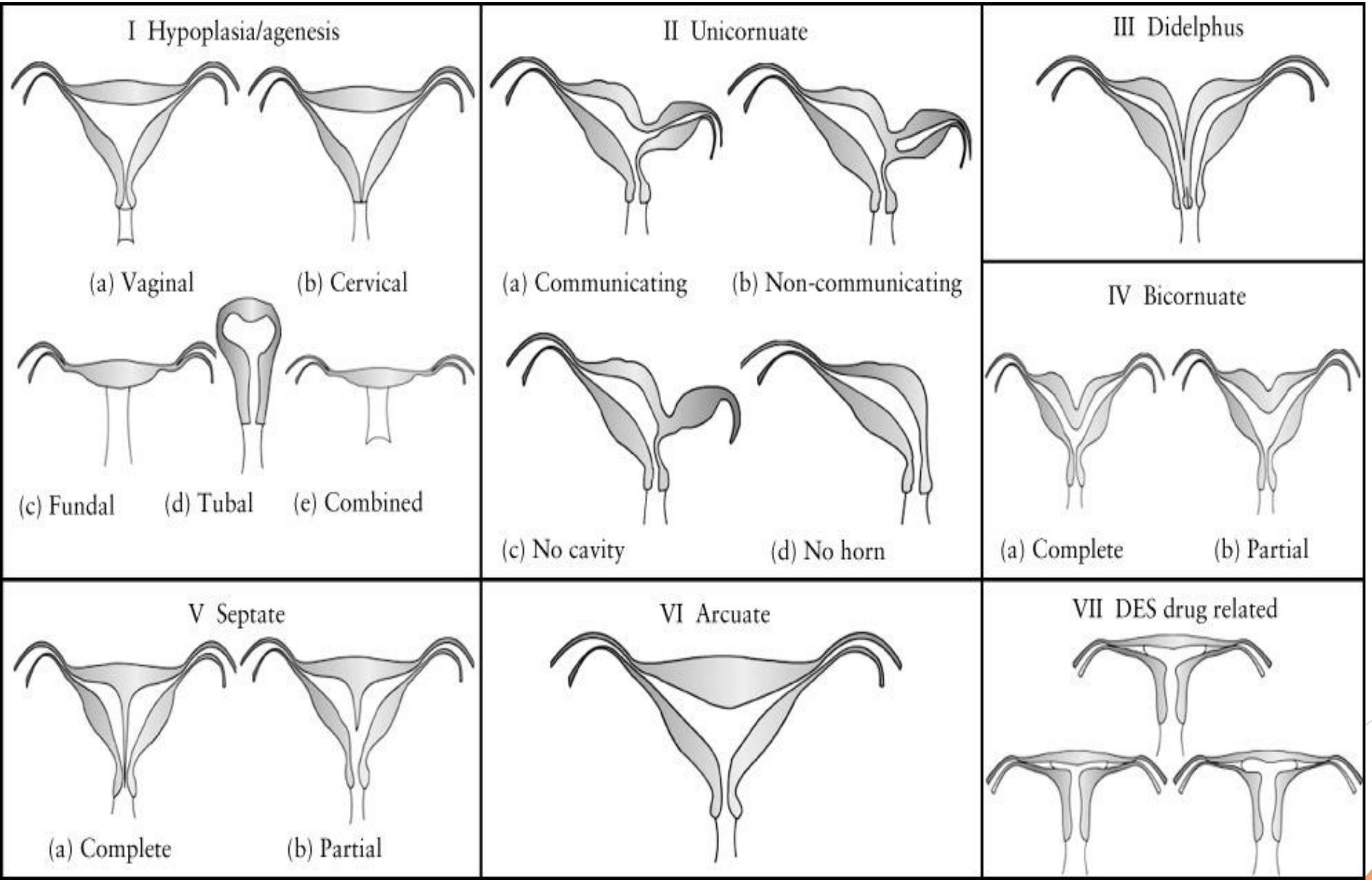
Class II Unicornuate

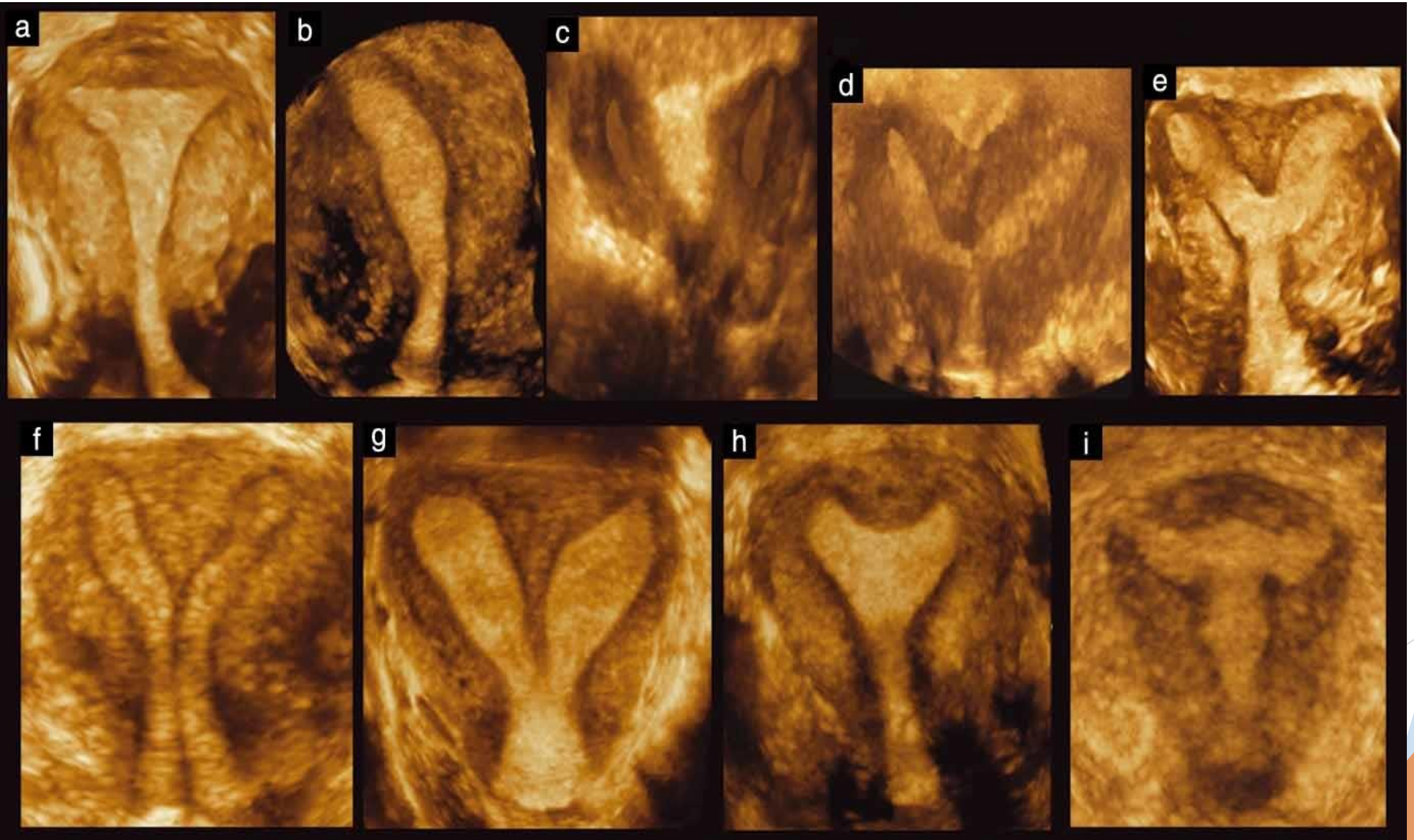
Class III Didelphys

Class IV Bicornuate

Class V Septate

Class VI Arcuate


I Hypoplasia/agenesis
(a) Vaginal
(b) Cervical
(c) Fundal
(d) Tubal
(e) Combined
II Unicornuate
(a) Communicating
(b) Non-communicating
(c) No cavity
(d) No horn
III Didelphus
IV Bicornuate
(a) Complete
(b) Partial
V Septate
(a) Complete
(b) Partial
VI Arcuate
VII DES drug related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- Acquired uterine malformations

- Submucous myomas,
- Endometrial polyps
- Uterine adhesions

What is the value of anatomical investigations in the diagnosis of RPL?

- All women with RPL should have an assessment of the **uterine anatomy.**
- transvaginal 3D ultrasound (3D US)
- Sonohysterography (SHG)
- MRI

Thrombophilia

- HEREDITARY THROMBOPHILIA
- Factor V Leiden mutation,
- Prothrombin mutation,
- Protein C,
- Protein S
- Antithrombin deficiency.
- Methylenetetrahydrofolate reductase (MTHFR) mutation

What is the value of thrombophilia screening in women with RPL?

- Suggest not to screen for hereditary thrombophilia unless in the context of research, or in women with additional risk factors for thrombophilia.

- Antiphospholipid antibodies (lupus anticoagulant [LA],
- Anticardiolipin antibodies [ACA IgG and IgM]), after two pregnancy losses .
- Β2 glycoprotein

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

- anti-HY antibodies
- Cytokine testing
- Antinuclear antibodies (ANA) testing
- natural killer (NK)

Metabolic and endocrinologic factors

- Thyroid dysfunction
- Diabetes
- Polycystic ovary syndrome (PCOS)
- Ovarian reserve testing
- Luteal phase insufficiency
- Vitamin D deficiency

Does the quality of the male gametes contribute to RPL?

- In the male partner, it is suggested to assess life style factors (smoking, alcohol consumption, exercise pattern, and body weight).
- Assessing sperm DNA fragmentation in couples with RPL can be considered for explanatory purposes, based on indirect évidence

Infectious Factor

- Genital Ureaplasma (U. urealyticum)
- Mycoplasma (M. hominis)
- Toxoplasma gondii,
- Listeria monocytogenes,
- Campylobacter species,
- Herpes virus, and cytomegalovirus

REVIEW

OPEN

A new algorithm for the evaluation of recurrent pregnancy loss redefining unexplained miscarriage: review of current guidelines

Ralph S. Papas[a] *and William H. Kutteh*[b,c]

Purpose of review
Couples with recurrent pregnancy loss (RPL) are often referred to reproductive specialists to help determine the reason for their repeated losses. This review will help to develop a strategy that is effective in providing a diagnosis, efficient to administer, and cost-effective to the healthcare system.

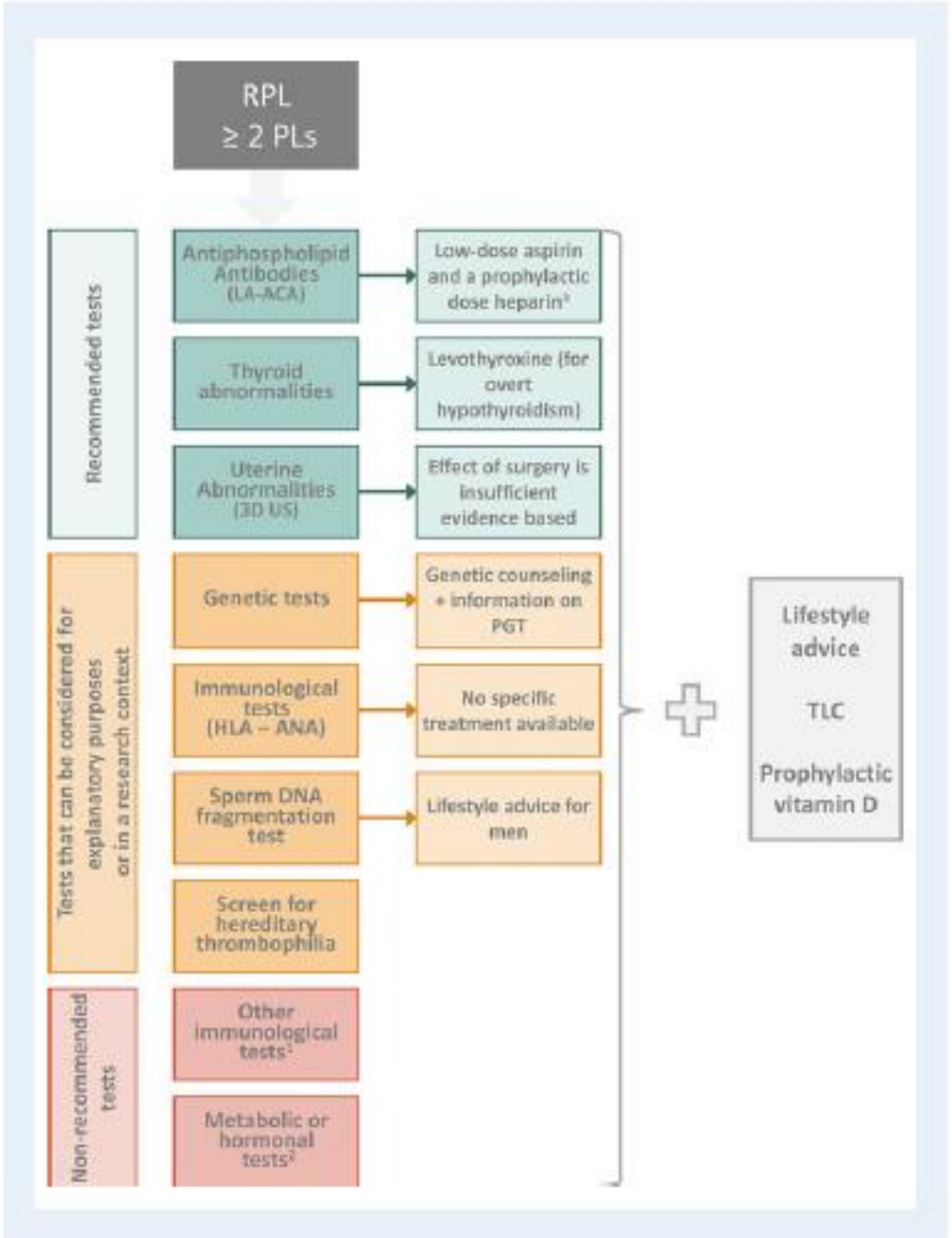
Recent findings
International societies have published different recommendations for the evaluation of RPL, they consider it appropriate to initiate an evaluation after two (or three) clinical miscarriages. On the contrary, the clinician who follows these guidelines will only be able to offer a possible explanation to fewer than half of the couples being evaluated. Recently, genetic testing of miscarriage tissue using 24-chromosome microarray (CMA) analysis at the time of the second pregnancy loss coupled with testing based on society guidelines has been shown provide an explanation in more than 90% of cases.

Summary
New guidelines for the complete evaluation of RPL should consider adding 24-CMA testing on the miscarriage tissue. Providing couples with an explanation for recurrent loss assists them in dealing with the loss and discourages the clinician from instituting unproven therapies. Truly unexplained pregnancy loss can be reduced to less than 10% with this new algorithm. Incorporation of these strategies will result in significant cost savings to the healthcare system.

Keywords

Table 1. Summary of the current guidelines from the Royal College of Obstetricians and Gynaecologists, American Society for Reproductive Medicine, and European Society of Human Reproduction and Embryology compared with the new proposed algorithm for the evaluation of recurrent pregnancy loss

Screening test	Royal College 2011	ASRM 2012	ESHRE 2017	PROPOSED 2020
Parental karyotyping	Not recommended Unless POC reveals unbalanced translocation	Recommended	Conditional recommendation: Only after 'individual risk assessment'[a]	Not Recommended Unless POC CMA reveals unbalanced translocation
POC cytogenetic analysis	Recommended (after third and subsequent miscarriage)	Not recommended (karyotype analysis of POC only in the setting of ongoing therapy for RPL)	Conditional recommendation: for explanatory purposes (strong recommendation to use CMA when POC genetic analysis is performed)	Recommend: Use CMA for the second and subsequent pregnancy loss
Uterine anatomy evaluation	Recommended: If Pelvic ultrasound abnormal get Hysteroscopy or 3D ultrasound	Recommended: 3D ultrasound Hystero-salpingogram Hysteroscopy	Strong recommendation: (conditional recommendation: prefer 3D ultrasound)	Recommend: 3D ultrasound
Antiphospholipid antibodies	Recommended: lupus anticoagulant and anticardiolipin antibodies	Recommended: lupus anticoagulant Anticardiolipin antibodies Antiβ2 glycoprotein I	Strong recommendation: lupus anticoagulant and anticardiolipin antibodies Good clinical practice: antiβ2 glycoprotein I	Recommend: lupus anticoagulant, anticardiolipin antibodies, antiphosphtidyl serine antibodies
Thyroid function	Recommended: TSH	Recommended: TSH Not recommended: TPO	Strong recommendation: TSH and TPO antibodies	Recommend: TSH TPO when TSH > 2.5 mIU/l
Prolactin	Not discussed	Recommended	Conditional recommendation: if hyperprolactinemia (oligo- or amenorrhea)	Recommended
Hemoglobin A1c	Recommended	Recommended to evaluate for diabetes	Not recommended	Recommended
Hereditary thrombophilia	Not recommended for first trimester (recommended for second trimester loss)	Only recommended if a personal or strong family history of thrombosis or thrombophilia	Conditional recommendation: Only in the context of research or in women with additional risk factors[a]	Only recommended if a personal or strong family history of thrombosis or thrombophilia
Sperm DNA fragmentation	Not discussed	Not recommended Controversial data	Conditional recommendation: only for explanatory purposes	Not recommended
PCOS and insulin resistance	Insufficient evidence	Not recommended Controversial data	Not recommended	Not Recommended


RPL
≥ 2 PLs
Recommended tests
Antiphospholipid Antibodies (LA-ACA)
Low-dose aspirin and a prophylactic dose heparin[3]
Thyroid abnormalities
Levothyroxine (for overt hypothyroidism)
Uterine Abnormalities (3D US)
Effect of surgery is insufficient evidence based
Tests that can be considered for explanatory purposes or in a research context
Genetic tests
Genetic counseling + information on PGT
Immunological tests (HLA – ANA)
No specific treatment available
Sperm DNA fragmentation test
Lifestyle advice for men
Screen for hereditary thrombophilia
Non-recommended tests
Other immunological tests[1]
Metabolic or hormonal tests[2]
Lifestyle advice
TLC
Prophylactic vitamin D

Thank you

For your attention