Recurrent Pregnancy Loss – a distinct clinical entity

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Genea fertilitySA WORLD LEADING FERTILITY

GYNAECOLOGY AND REPRODUCTIVE CARE

FLINDERS MEDICAL CENTRE

Government of South Australia SA Health

St Andrew's Hospital

Kate, 30 years old and Andrew, 32 years old

Trying to conceive for 3 years (from age 27/29)

4 pregnancy losses since started trying G4P0:
G1 – US @ 8/40 – empty sac
G2,G3 – pos urine hCG -> bleeding
G4 – serum hCG 250 ->15 -> bleeding

Emotionally exhausted and anxious

Not sure if can carry pregnancy

Keen to get some answers

WHY???

What are our chance for healthy pregnancy?

What tests do we need to complete?

What treatments can help?

Pregnancy loss is significant negative life event

Repetitive nature – intensifies the grief experienced by women/couples

Before trying to conceive, most couples want an explanation for their losses and are keen on treatments that will prevent a recurrence

Investigation will reveal possible causes < 50% of couples -> the majority will not be given a satisfactory explanation

- Devastating for the patients and their families
- Frustrating for the medical practitioners

ASRM PAGES

Evaluation and treatment of recurrent pregnancy loss: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama Fertil Steril® 2012;98:1103–11.

Published Online 19 June 2023

DOI: 10.1111/1471-0528.17515

BJOG An International Journal of Obstetrics and Gynaecology

RCOG GREEN-TOP GUIDELINES

Recurrent Miscarriage

Green-top Guideline No. 17

Royal College of Obstetricians & Gynaecologists

eshre

Recurrent Pregnancy Loss

Guideline of European Society of Human Reproduction and Embryology

Update 2022

ESHRE Recurrent Pregnancy Loss Guideline Development Group

Recurrent Pregnancy Loss (RPL) – Definition and Terminology have changed

- **Recurrent Pregnancy Loss** vs. Recurrent Miscarriage
- A diagnosis of RPL could be considered after the **loss of two or more pregnancies**
- A pregnancy in the definition is **confirmed at least by either serum or urine b-hCG** (including nonvisualized pregnancy losses)
- Ectopic and molar pregnancies or Implantation failure are not included
- Recurrent "Early" Pregnancy Loss (REPL) is the loss of two or more pregnancies before 10 weeks of gestational age

RPL – Incidence

- Sporadic (single) pregnancy loss - 15 – 20% of couples
- Two pregnancy losses – 3%
- Three or more pregnancy losses – 1%

The average observed incidence of RPL is higher than what would be expected by chance alone

- 1st Trimester – 75%
  - Implantation to 6 weeks – 1/3 of all 1st Trim losses
- 2nd Trimester 25%

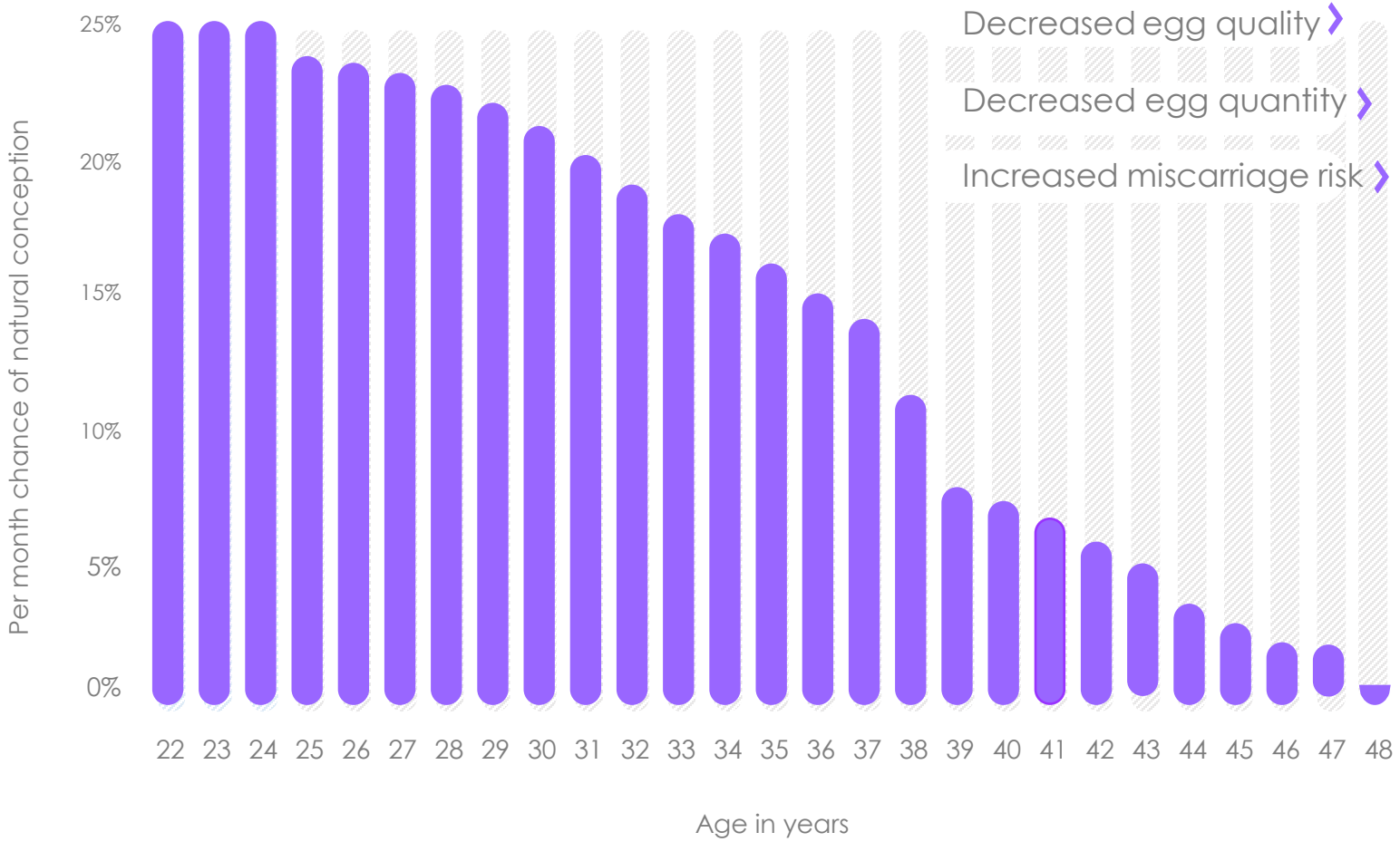
The woman's risk of miscarriage is directly related to the outcomes of previous pregnancies

- Subsequent pregnancy loss rate:
  - After 1: 21%
  - After 2: 26%
  - After 3: 40-50% (30-33% if previous live birth)
  - Higher with advancing maternal age

RPL – Risk Factors

- Age
- Environmental exposures
- Stress?
- Obesity
- Lifestyle:
  - Smoking
  - Illicit drug use
  - ETOH
  - Caffeine consumption (dose-dependent)
- Congenital uterine abnormalities
- Acquired Thrombophilia:
  - Anti-phospholipid syndrome
- Poorly controlled diabetes
- Poorly controlled thyroid
- Parental aneuploidies

- RPL – Age is the main Risk Factor



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AGE AND FERTILITY

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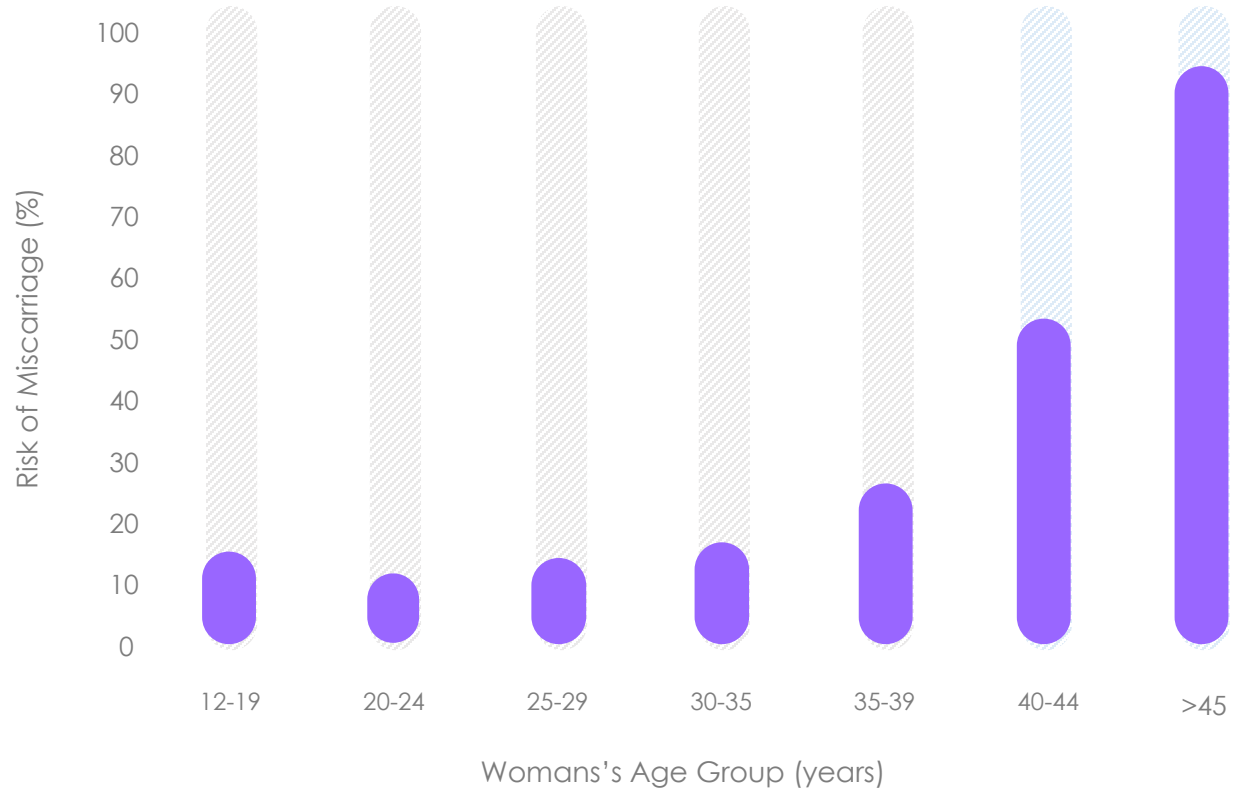
RISK OF MISCARRIAGE BY AGE



Live Birth Rate per IVF cycle

BY AGE

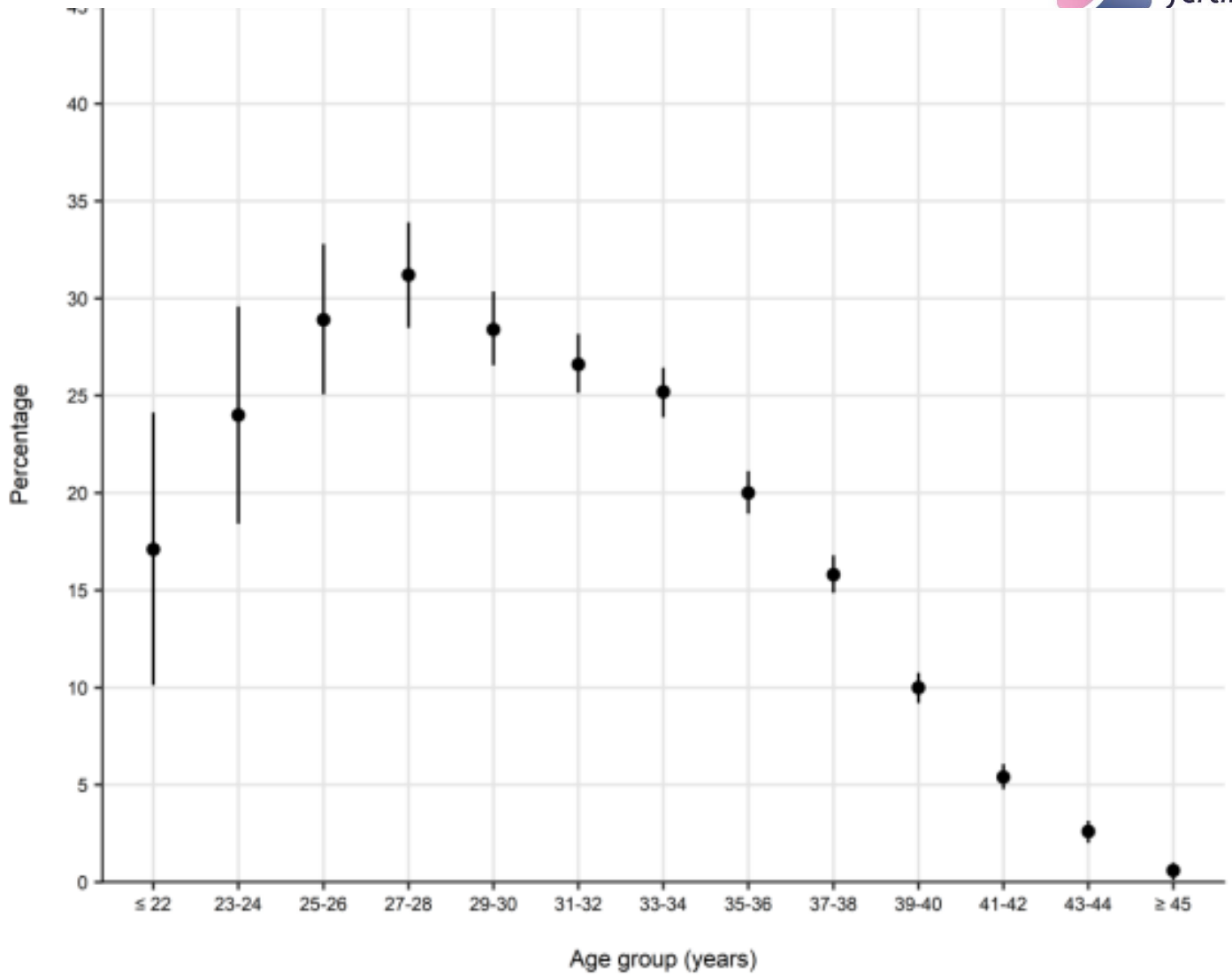
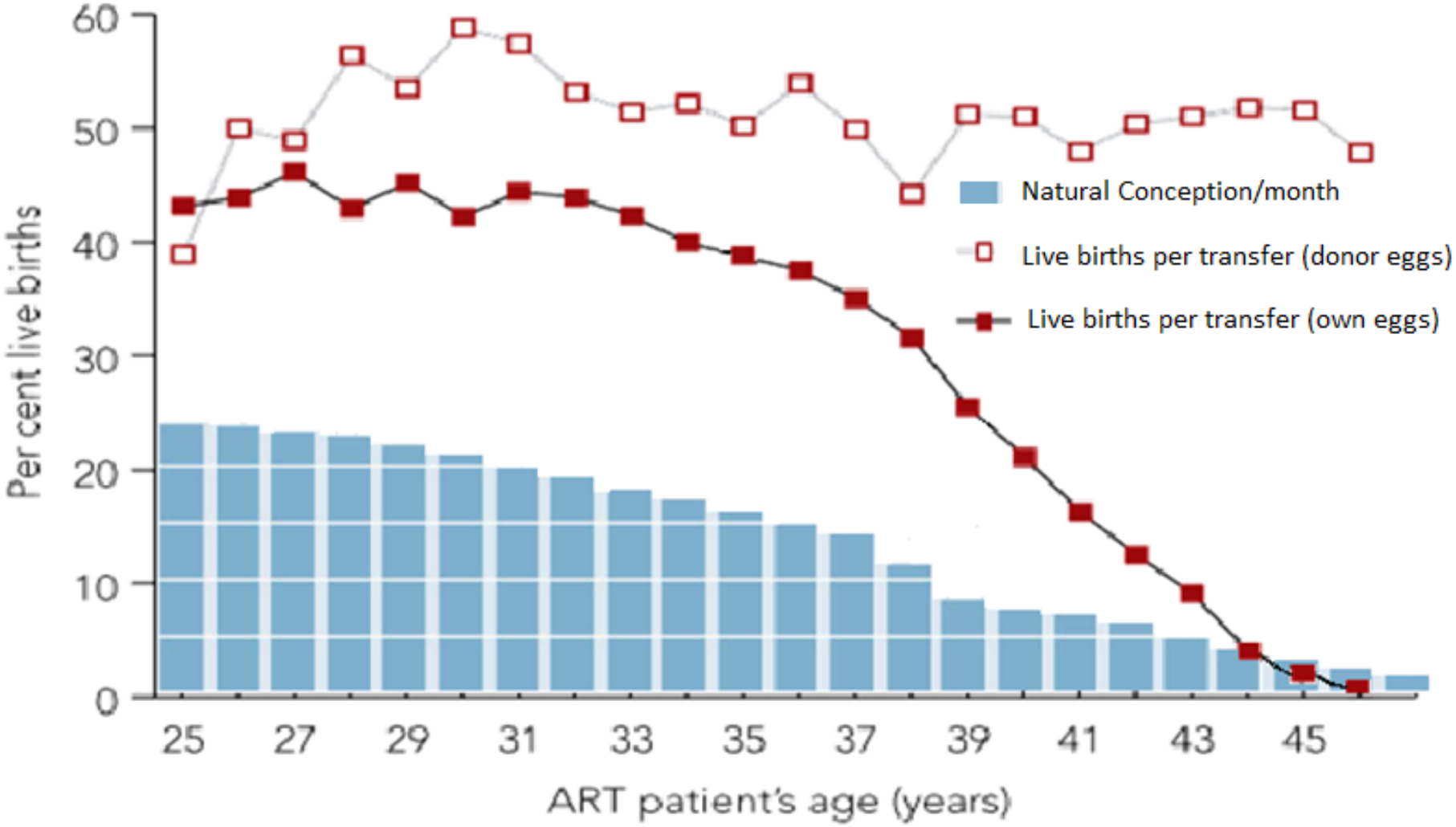


Figure 3: Live birth rate (with 95% confidence intervals) per initiated autologous fresh cycle (excluding freeze-all) by female patient's age at start of a treatment cycle, Australia and New Zealand, 2020

ART data



2003 Assisted reproductive technology success rates: national summary and fertility clinic reports.

RPL – Age is the main Risk Factor

Computer simulation fertility model (data on the chance of age-dependent pregnancy loss):

- To achieve a two-children family -> couples should start trying to conceive when the female partner **≤ 31 years** or **no later than 27 years if IVF is not an option** (at least 90% chance)

- To achieve a one-child family -> couples should start trying to conceive when the female partner **≤ 35 years** or **no later than 32 years if IVF is not an option** ***Habbema et al.,*** *2015*

Advanced female age is a well-established risk factor for female subfertility, fetal anomalies, stillbirth, and obstetric complications ***Nybo Andersen et al.,*** *2000,* ***Sauer,*** *2015*

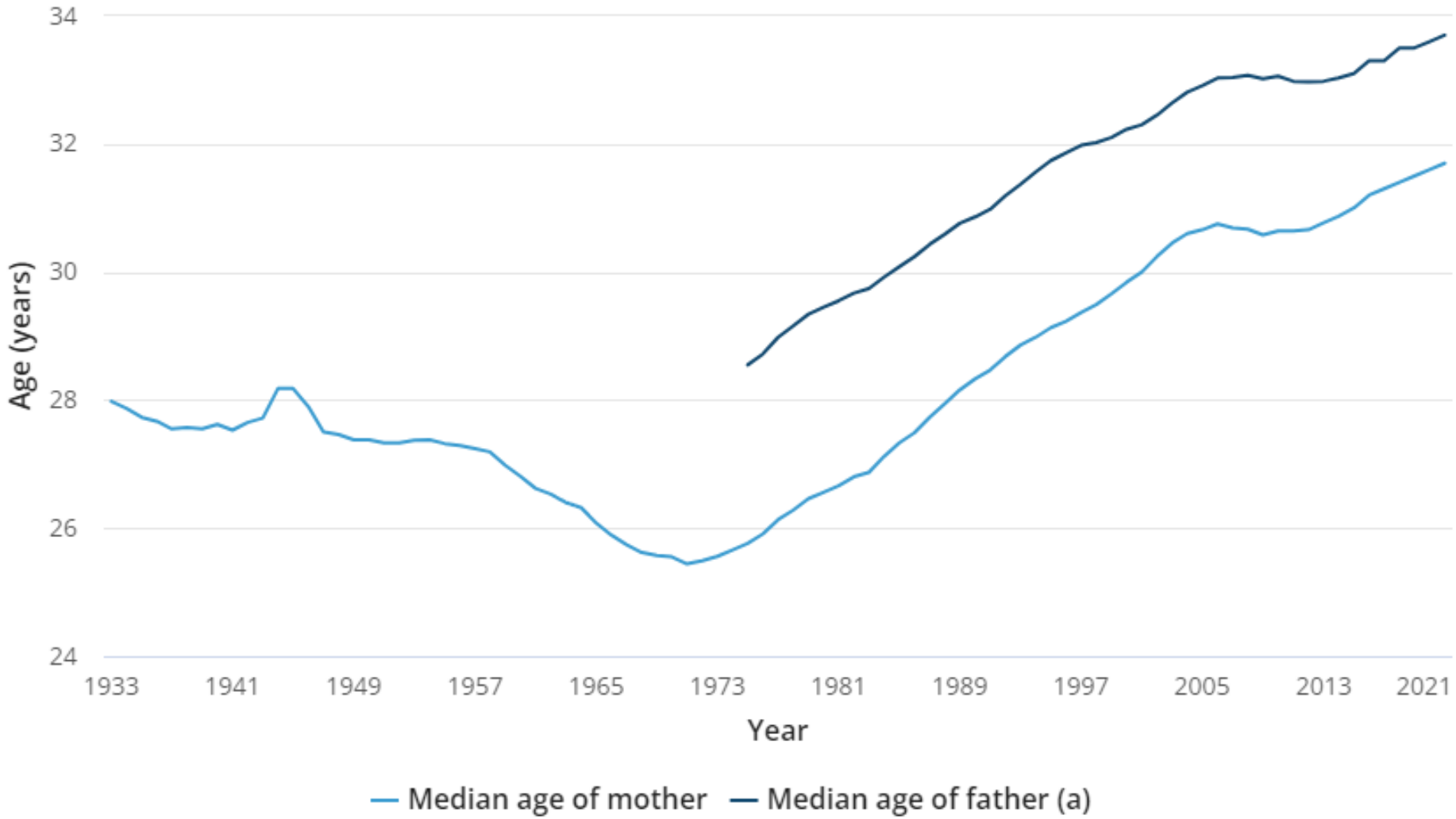
Most studies evaluating male age have reported a significant association between increasing male age and the incidence of miscarriage

There are no studies on male age and RPL

Median age of parents 1933 - 2021

For births registered in 2021, the median age of:

- mothers was 31.7 years
- fathers was 33.7 years.



Recommendations

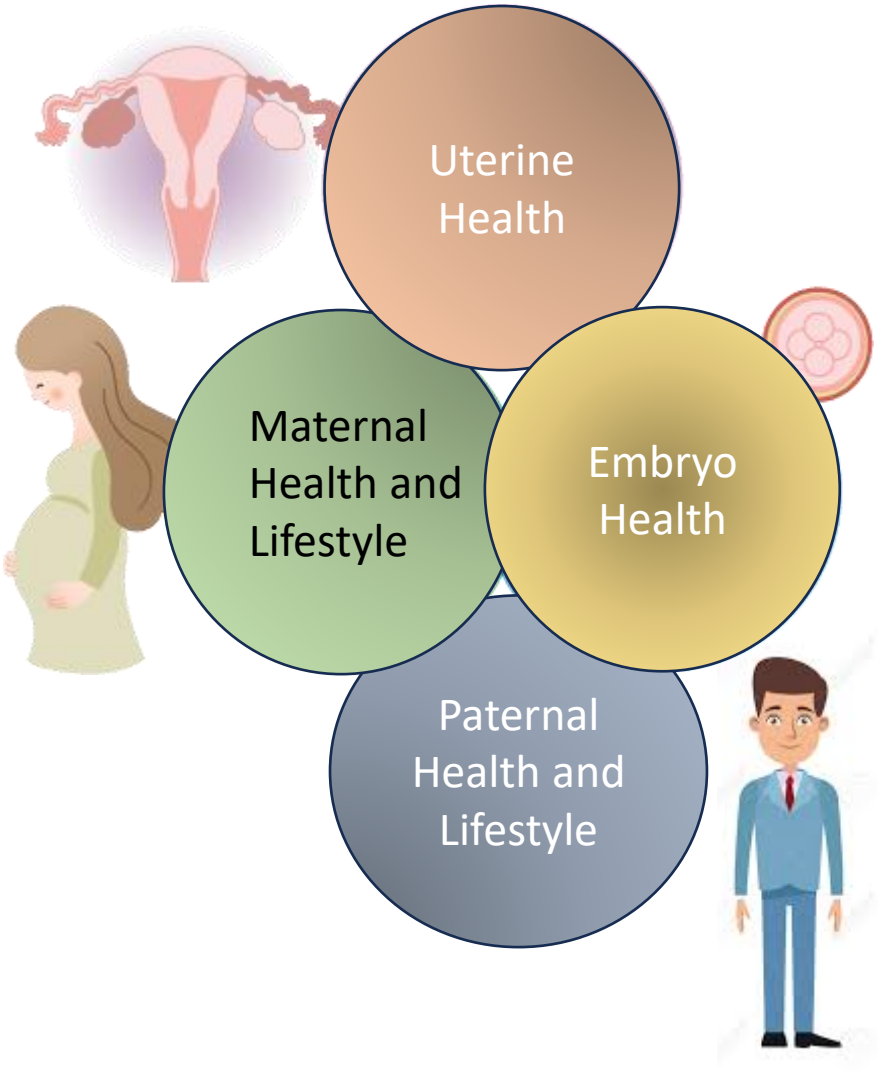
Women should be sensitively informed that the risk of pregnancy loss is lowest in women aged 20 to 35 years.	Strong	⊕⊕■■
Women should be sensitively informed that the risk of pregnancy loss rapidly increases after the age of 40.	Strong	⊕⊕■■
Stress is associated with RPL, but couples should be informed that there is no evidence that stress is a direct cause of pregnancy loss.	Strong	⊕■■■

Overall, the studies indicate that there is an association between stress and pregnancy loss,
but they provide no information on whether the stress is a result of RPL, or whether stress could be a causal factor in RPL.

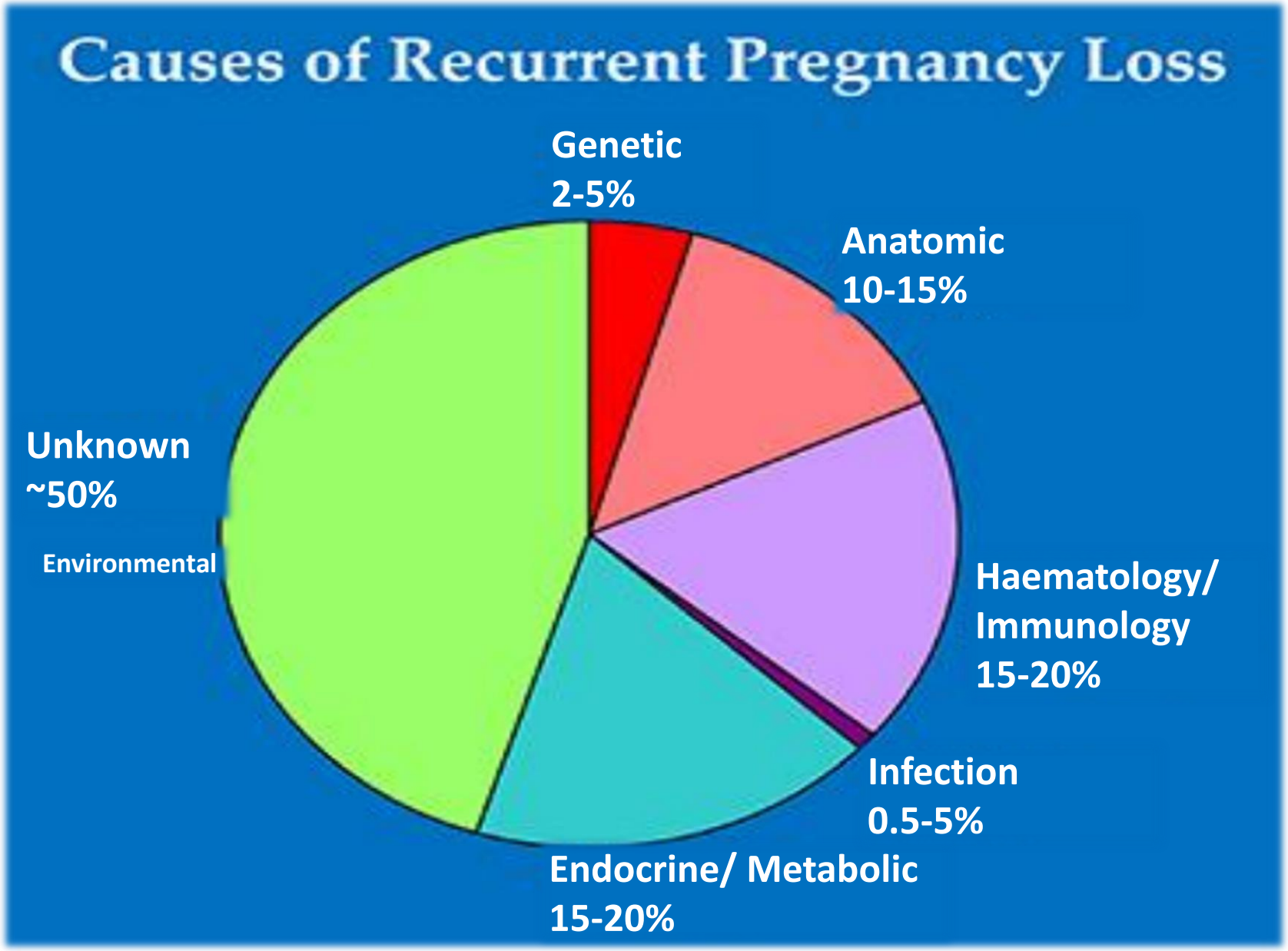
Environmental Exposures

Based on only a few small studies, exposure to occupational and environmental factors
(heavy metals, pesticide, lack of micronutrients) is associated with an increased risk of pregnancy loss in women with RPL.
Exposure to possible hazardous substances should be avoided during pregnancy (for all pregnant women),
there are insufficient data to recommend protection against a certain occupational or environmental factor to prevent RPL.

Recurrent Pregnancy Loss – Clinical Approach



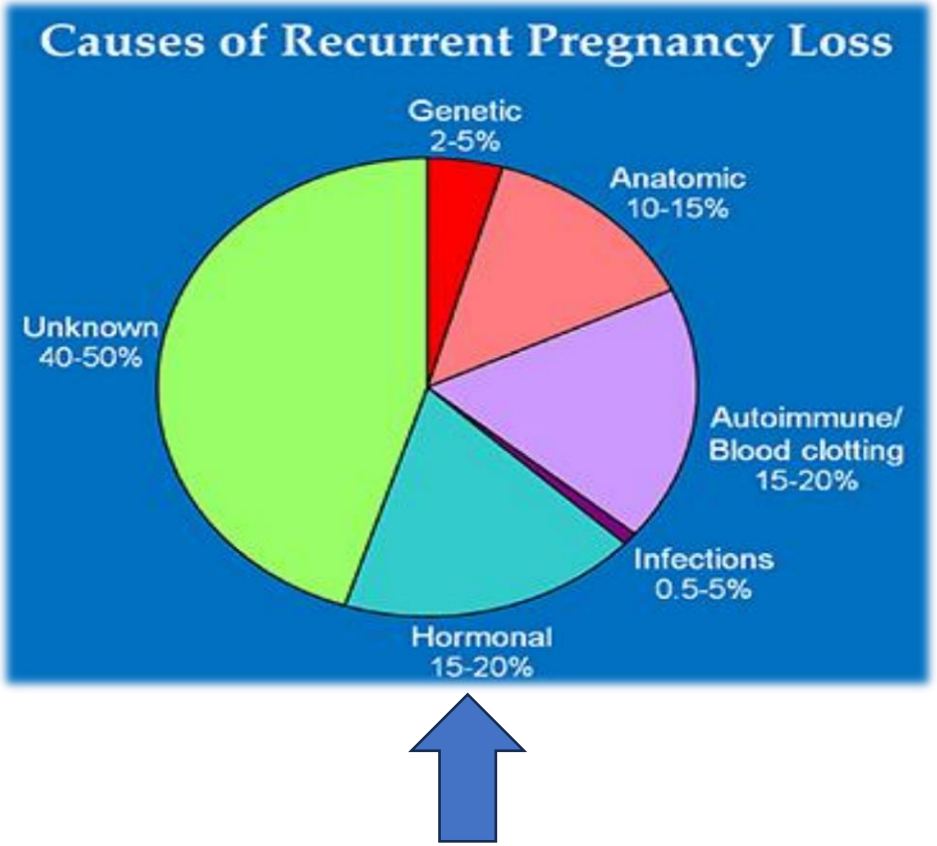
The decision on when to start investigations will have to be decided with the couple, as the result of shared decision-making



- As number of losses increases, greater likelihood of cause

Endocrine & Metabolic causes (15-20%)

- Luteal phase defect
- Endocrine Conditions:
  - Thyroid disease
  - Hyperprolactinemia
  - PCOS
- Metabolic derangements
  - Hyperinsulinaemia
  - Obesity



Luteal Phase Defect (LPD)

- A progesterone-related problem, causing euploid miscarriage
- The corpus luteum in the ovary produces progesterone during early pregnancy
  - Essential direct effect on decidua & myometrium
  - Inhibits lymphocyte cytotoxicity, modulates function of endometrial/ peripheral NK cells, promotes release of Th2 over Th1 cytokines from T cells
- Defect in the function of the corpus luteum -> low Prog levels -> increased risk of miscarriage
  - Aberrant FSH & LH secretion early in the cycle -> abnormal folliculogenesis
  - LH surge timing (too early, too late)
  - Insufficient oestrogen production to allow normal progesterone action
- There is no clear definition for LPD, and there are certainly no reliable tests to identify patients who may have the condition
- Serum and salivary progesterone – unclear the diagnostic and prognostic value
- Histologic assessment of the endometrium - high inter-/intraobserver variation; low diagnostic value

Stephenson et al., *Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case-control study. Hum Reprod. 2002;**17**:446–451.* ***Pillai et al.,*** *Role of serum biomarkers in the prediction of outcome in women with threatened miscarriage: a systematic review and diagnostic accuracy meta-analysis. Hum Reprod Update. 2016;**22**:228–239.* ***Tulppala et al.,*** *Luteal phase defect in habitual abortion: progesterone in saliva. Fertil Steril. 1991;**56**:41–44.* ***Daya et al.,*** *Progesterone profiles in luteal phase defect cycles and outcome of progesterone treatment in patients with recurrent spontaneous abortion. Am J Obstet Gynecol. 1988;**158**:225–232.* ***Noyes, et al.,*** *1950*

Luteal Phase Defect (LPD)

- Direction of causality? - > is low Progesterone the cause or effect of a miscarriage?
- Inconsistent evidence and no clear value for prognosis and treatment

Recommendation

Luteal phase insufficiency testing is not recommended in women with RPL.	Strong ⊕⊕■■

Justification

	Association	Contributing factor	Prognosis	Treatment
Luteal phase insufficiency testing*	Inconsistent	No data	No	possible

** Midluteal progesterone or endometrial biopsy*

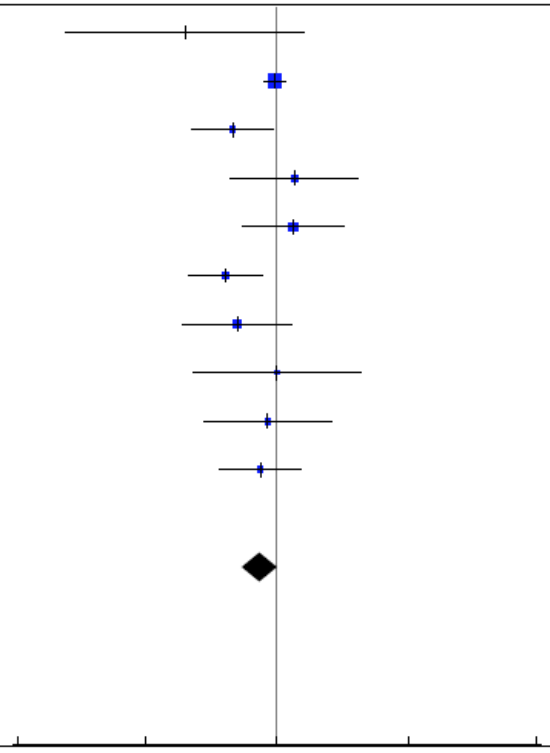
Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology

David M Haas, Taylor J Hathawa

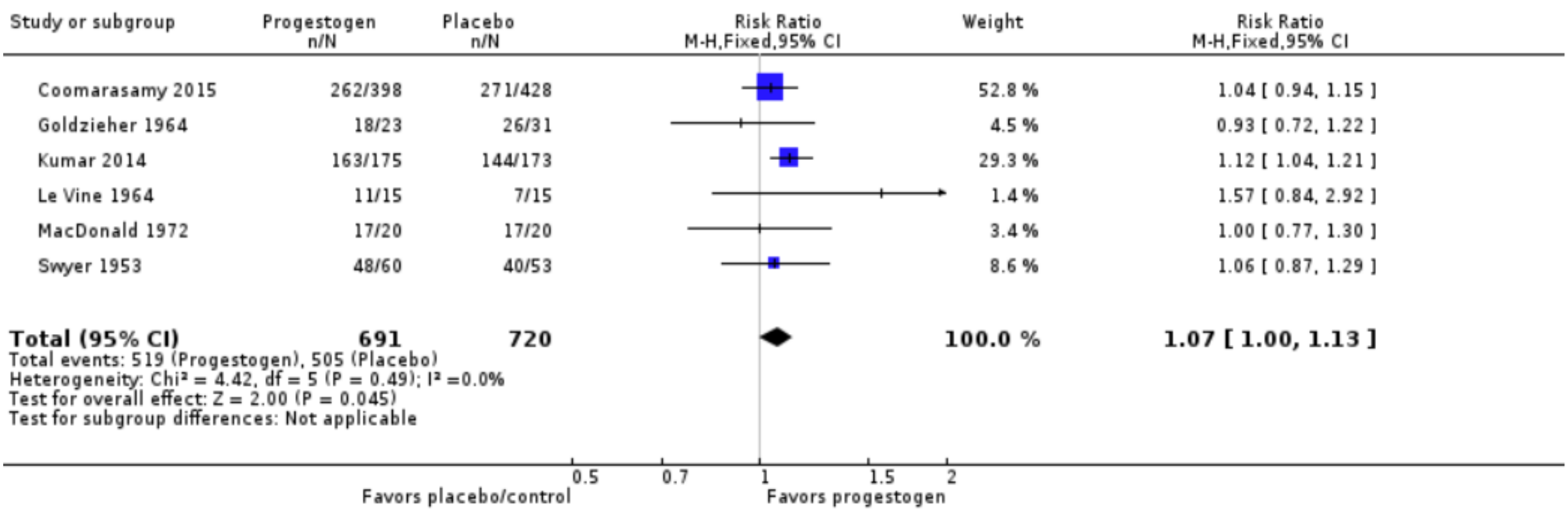
Version published: 20 November 2019 V
https://doi.org/10.1002/14651858.CD00

Analysis 1.1. Comparison 1 Progestogen versus placebo/no treatment, Outcome 1 Miscarriage (all trials).

Study or subgroup	Progestogen n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Agarwal 2016	1/30	5/30		2.04%	0.2[0.02,1.61]
Coomarasamy 2015	128/398	143/428		28.08%	0.96[0.79,1.17]
El-Zibdeh 2005	11/82	14/48		11.93%	0.46[0.23,0.93]
Goldzieher 1964	5/23	5/31		6.15%	1.35[0.44,4.11]
Klopper 1965	8/18	5/15		8.81%	1.33[0.55,3.22]
Kumar 2014	12/175	29/173		13.42%	0.41[0.22,0.78]
Le Vine 1964	4/15	8/15		7.74%	0.5[0.19,1.31]
MacDonald 1972	3/20	3/20		3.84%	1[0.23,4.37]
Shearman 1963	5/27	5/23		6.23%	0.85[0.28,2.58]
Swyer 1953	11/60	13/53		11.76%	0.75[0.37,1.52]
Total (95% CI)	**848**	**836**		**100%**	**0.73[0.54,1]**
Total events: 188 (Progestogen), 230 (Placebo)					
Heterogeneity: Tau^2=0.08; Chi^2=14.53, df=9(P=0.1); I^2=38.05%					
Test for overall effect: Z=1.97(P=0.05)					



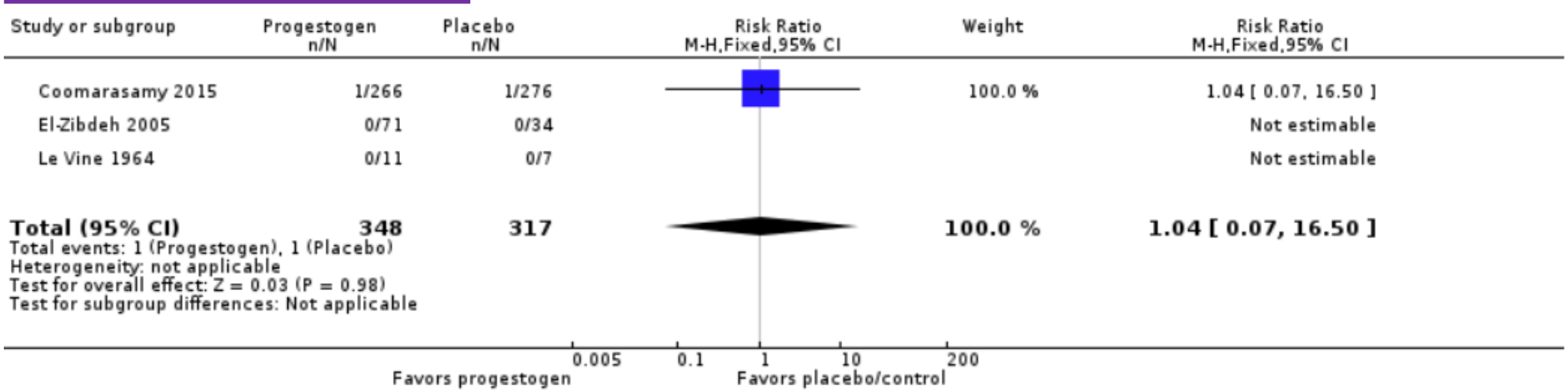
Review: Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology
Comparison: 1 Progestogen versus placebo/no treatment
Outcome: 5 Live birth rate



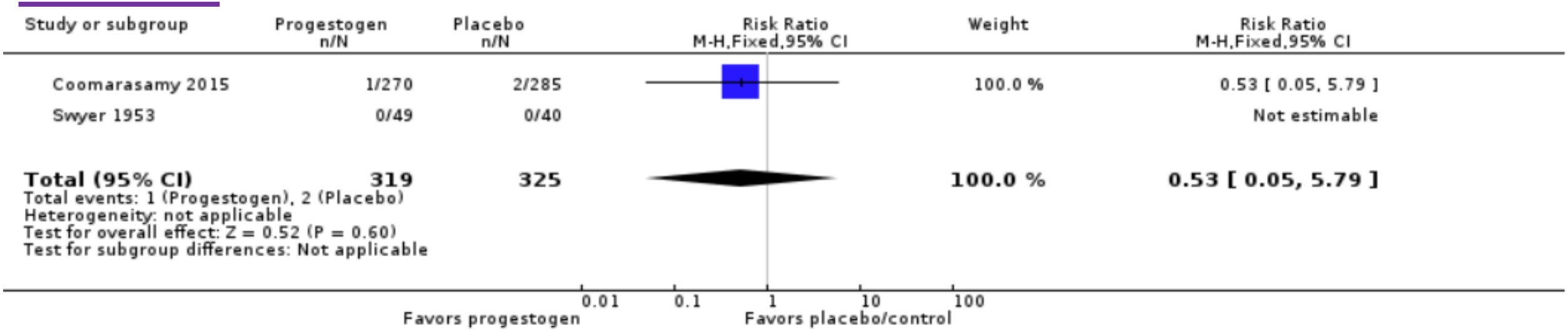
Authors' conclusions:

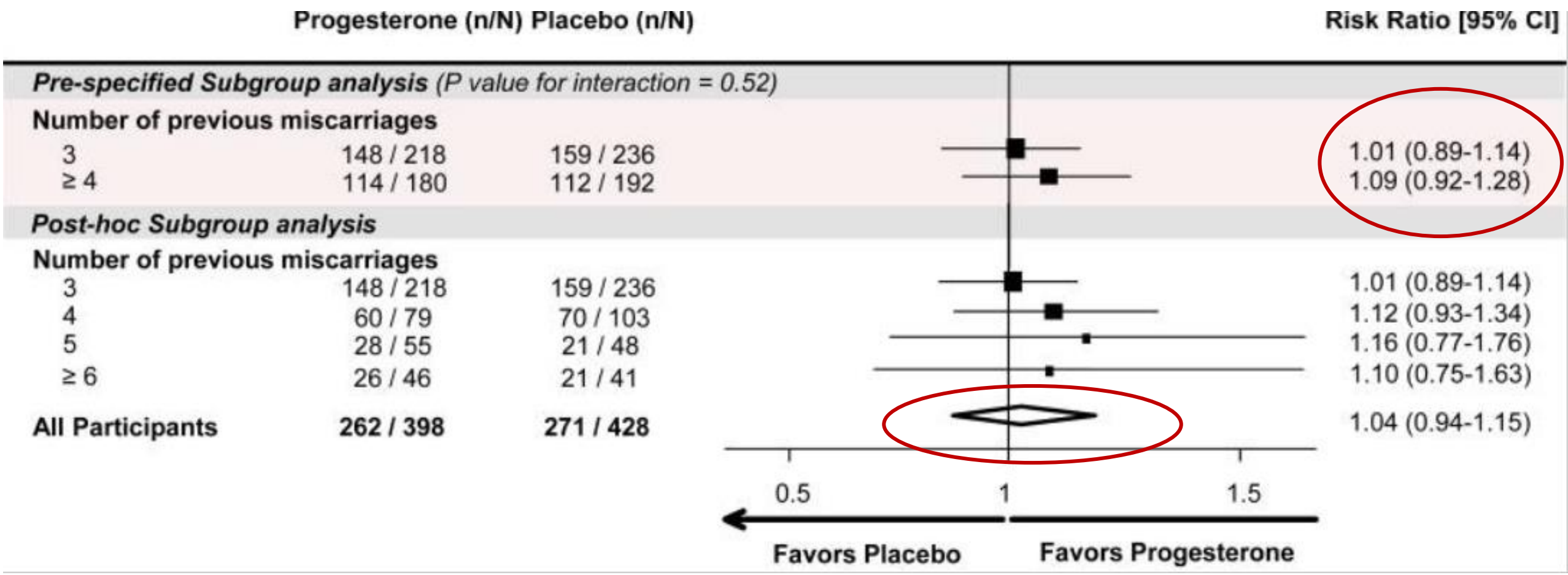
For women with unexplained recurrent miscarriages, supplementation with progestogen therapy may reduce the rate of miscarriage in subsequent pregnancies.

Review: Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology
Comparison: 1 Progestogen versus placebo/no treatment
Outcome: 8 Fetal genital abnormalities/virilization



Review: Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology
Comparison: 1 Progestogen versus placebo/no treatment
Outcome: 9 Stillbirth





PROMISE trial data on live birth >24 weeks by the number of previous miscarriages

CI, confidence interval; *PROMISE*, PROgesterone in recurrent MIScarriagE.

Coomarasamy A., Williams H., Truchanowicz E. A randomized trial of progesterone in women with recurrent miscarriages. *N Engl J Med.* 2015;**373**:2141–2148.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

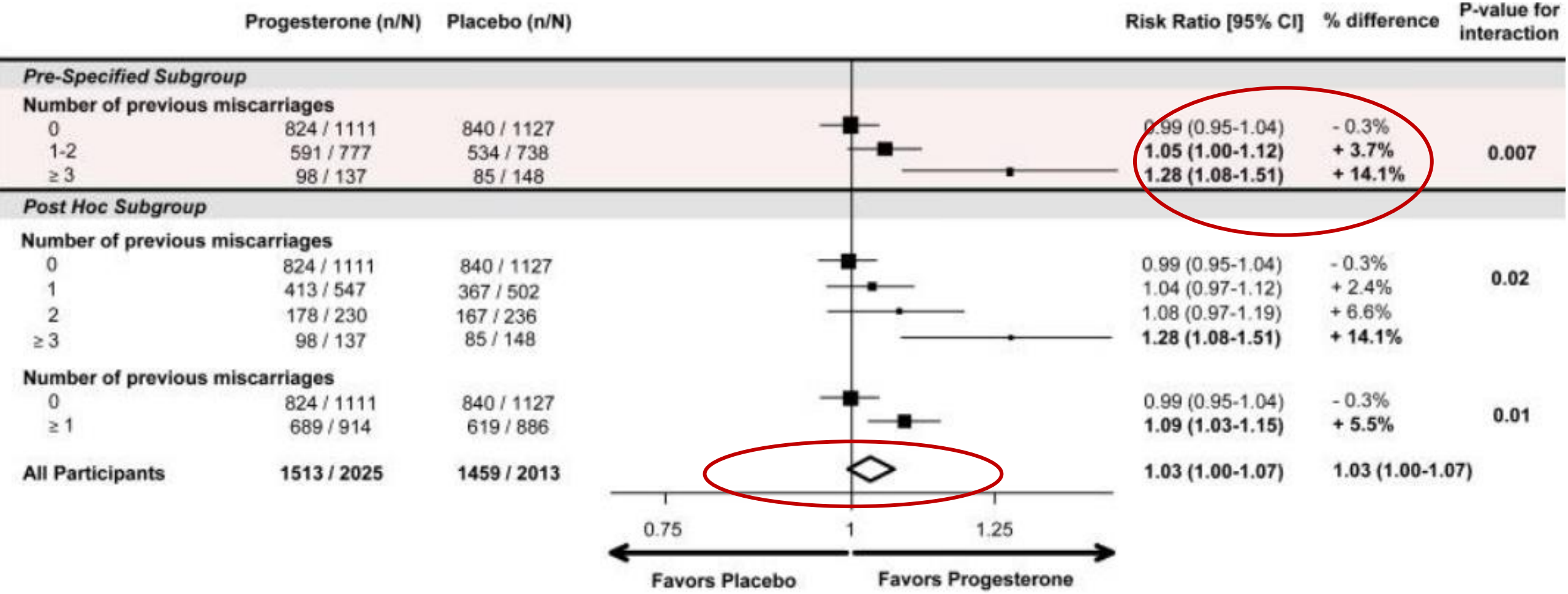
A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy

A. Coomarasamy, A.J. Devall, V. Cheed, H. Harb, L.J. Middleton, I.D. Gallos, H. Williams, A.K. Eapen, T. Roberts, C.C. Ogwulu, I. Goranitis, J.P. Daniels, A. Ahmed, R. Bender-Atik, K. Bhatia, C. Bottomley, J. Brewin, M. Choudhary, F. Crosfill, S. Deb, W.C. Duncan, A. Ewer, K. Hinshaw, T. Holland, F. Izzat, J. Johns, K. Kriedt, M.-A. Lumsden, P. Manda, J.E. Norman, N. Nunes, C.E. Overton, S. Quenby, S. Rao, J. Ross, A. Shahid, M. Underwood, N. Vaithilingam, L. Watkins, C. Wykes, A. Horne, and D. Jurkovic

N ENGL J MED 380;19 NEJM.ORG MAY 9, 2019

A multicenter, randomized, double-blind, placebo-controlled trial to evaluate progesterone, as compared with placebo, in women with vaginal bleeding in early pregnancy.
The PRISM Trial

Population	Women with vaginal bleeding during the first 12 weeks of pregnancy
Intervention	400 mg of micronized progesterone taken vaginally or rectally twice daily from randomization until 16 weeks of gestation
Comparison	Placebo
Primary outcome	Live birth ≥34 weeks
Sample size and power	4153 patients randomized, 90% power to pick up a 5% difference in live births
Hospitals	48 hospitals in the United Kingdom



PRISM trial data on live birth >34 weeks by the number of previous miscarriages

CI, confidence interval; *PRISM*, PRogesterone In Spontaneous Miscarriage.

Coomarasamy A., Devall A.J., Cheed V. A randomized trial of progesterone in women with bleeding in early pregnancy. *N Engl J Med.* 2019;**380**:1815–1824.

Thyroid Dysfunction

- Thyroid hormones are essential for fetal development
- Thyroid hormone disorders are associated with abnormal folliculogenesis, spermatogenesis, fertilization and embryogenesis
- Positive anti-thyroid Abs (TPO Ab) and subclinical hypothyroidism (TSH > 2.5 mIU/L with normal FT3/FT4) are associated with RPL, but it is uncertain if treatment helps

Recommendations

Thyroid screening (TSH and TPO antibodies) is recommended in women with RPL.	Strong	⊕⊕⊕■
Abnormal TSH levels should be followed up by T4 testing in women with RPL.	Strong	⊕⊕⊕■

Hyperprolactinemia

- Prolactin is a hormone essential for female reproduction
- Prolactin plays a role in maintaining corpus luteum, and progesterone secretion – mechanism still unclear
- High Prolactin is possibly associated with PCOS, LPD, stress and obesity
- Association with RPL is inconsistent

Recommendation

Prolactin testing is not recommended in women with RPL in the absence of clinical symptoms of hyperprolactinemia (oligo/amenorrhea).	Conditional	⊕⊕■■

PCOS and abnormal Insulin metabolism

- PCOS is associated with GDM, PET, PIH; association with RPL is uncertain
- Insulin Resistance is more prevalent in women with RPL, but mechanism is unclear
- Well controlled DM is not a risk factor

	Association	Contributing factor	Prognosis	Treatment
PCOS	YES	YES	NO	Metformin for sporadic PL no studies for RPL
Insulin resistance*	YES (OR 3.6)	Unclear	No studies	No studies
Fasting insulin	Inconsistent (2 YES, 1 NO)	Unclear	No studies	No studies
Fasting glucose	NO	NO	No studies	No studies

Recommendation

Assessment of PCOS, fasting insulin and fasting glucose is not recommended in women with RPL to improve next pregnancy prognosis.	Strong	⊕⊕■■

Obesity

Recommendation

Couples with RPL should be informed that maternal obesity or being significantly underweight is associated with obstetric complications and could have a negative impact on their chances of a live birth and on their general health.	Strong	⊕⊕■■
Striving for a healthy normal range BMI is recommended.	GPP	

Justification

Maternal obesity is a strong risk factor in RPL, but there are no studies evaluating the impact of weight loss on subsequent PL. However, weight loss has a positive impact on fertility outcomes and reduced weight is associated with reduced complications during pregnancy and birth and reduced cardiovascular and diabetic morbidity and mortality. The GDG formulated a strong recommendation for information provision and for striving for a healthy normal BMI (20-25 kg/m^2 for Caucasians).

There are no studies evaluating the impact of male weight on RPL

Other endocrine/ metabolic

Recommendation

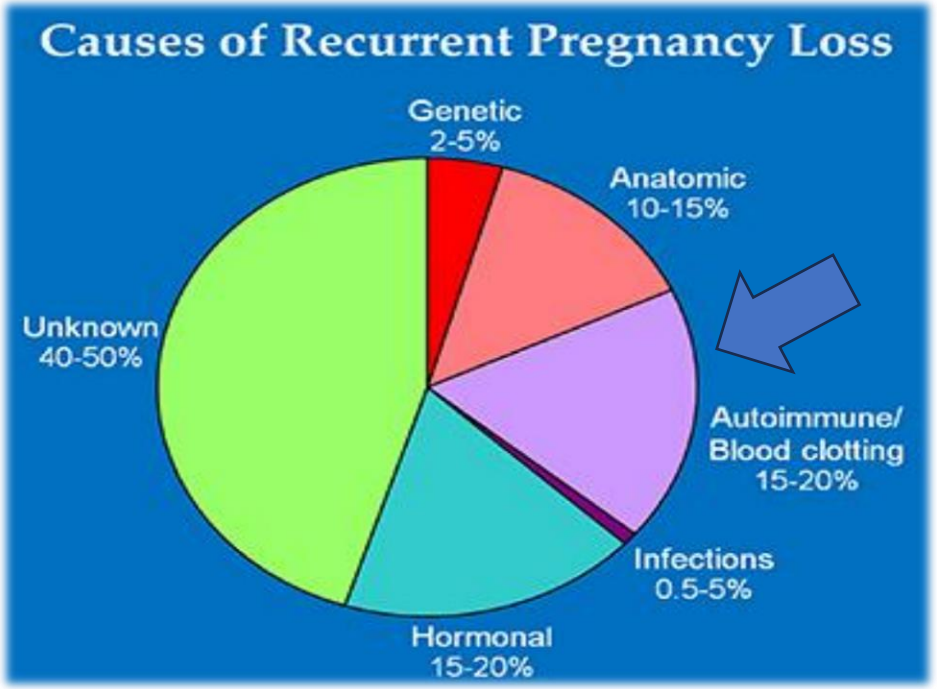
Androgen testing is not recommended in women with RPL.	Strong	⊕⊕■■
LH testing is not routinely recommended in women with RPL	Strong	⊕■■■
Ovarian reserve testing is not routinely recommended in women with RPL.	Strong	⊕⊕■■
Measurement of homocysteine plasma levels is not routinely recommended in women with RPL.	Strong	⊕■■■

	Association	Contributing factor	Prognosis	Treatment
Vitamin D	Possible	Possible	/	Vitamin D supplementation

Chronic liver/ renal disease, DM (poorly controlled), Wilson's disease have been associated with RPL

Haematology/ Immunology (15-20%)

- Thrombophilia
  - Hereditary
    - Factor V Leiden
    - Prothrombin mutation
    - MTFHR mutation
    - Protein C/ Protein S/ Antithrombin III deficiency
  - Acquired
    - Antiphospholipid Syndrome (APS)
      - Lupus anticoagulant (LA),
      - anticardiolipin antibodies (ACA, IgG and IgM),
      - β2 glycoprotein I antibodies (aβ2GPI, IgG and IgM)
- Immunological conditions
  - Human Leucocyte Antigen (HLA)
  - Cytokines
  - Antinuclear antibodies (ANA)
  - Natural killer cells (NK cells)
  - Coeliac Disease
  - Anti-sperm antibodies



Hereditary Thrombophilias

(Factor V Leiden, prothrombin, protein C and protein S and antithrombin deficiencies)

- Prospective trials have not confirmed that these are associated with first trimester losses (Dizon-Towson et al. Obstet Gynecol 2005 Silver RM et al. Obstet Gynecol 2010)
- Recent RCT failed to show benefit of treatment

THE LANCET The Lancet, Early Online Publication, 25 July 2014

Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial

36 tertiary care centres in five countries Between Feb 28, 2000, and Sept 14, 2012, 292 women both thrombophilia and a history of either adverse pregnancy outcomes or venous thromboembolism 25 of 146 women (17·1%) in the dalteparin group versus 27 of 143 (18·9%) in the control group

- May be clinically justified when a patient has a personal history of VTE

Hereditary Thrombophilia

Recommendation

For women with RPL, we suggest not to screen for hereditary thrombophilia unless in the context of research, or in women with additional risk factors for thrombophilia.	Conditional ⊕⊕⊕■

Justification

	Association	Contributing factor	Prognosis	Treatment
Hereditary thrombophilia*	No/weak	Unclear	Yes	No

**** This includes Factor V Leiden mutation - Prothrombin mutation - MTHFR mutation - Protein C, Protein S and Antithrombin deficiency***

If screening is performed, it is recommended to postpone until 6 weeks after the pregnancy (loss) (Protein C, Protein S, AT III)

Acquired Thrombophilia

- Hyperhomocystinaemia (MTHFR gene mutation)
- Antiphospholipid Ab (APS) - 11% to 42% of RPL (5% of general population)
  - APS – diagnosis by clinical criteria (*3 losses or severe PET, thrombosis, thrombocytopenia, ischaemic episode*) + laboratory criteria
  - LA increases the risk of pregnancy loss 3- to 4.8-fold, and ACA 1- to 20-fold
    - Implantation
      - binding to cytotrophoblast cells - **direct cellular injury** and impaired trophoblast invasion
      - binding on the surface anticoagulants expressed on trophoblastic cells with **inhibition of syncytia formation**.
      - Cellular damage may lead to thrombosis in the placental vessels and impairment of embryonic implantation
    - Post implantation
      - **Thrombogenic** action of APA with reduced placental perfusion

Acquired Thrombophilia

Recommendations

For women with RPL, we recommend screening for antiphospholipid antibodies (LA and ACA [IgG and IgM]), after two pregnancy losses.	Strong	⊕⊕■■
For women with RPL, screening for aβ2GPI can be considered after two pregnancy losses.	GPP	

Justification

	Association	Contributing factor	Prognosis	Treatment
Antiphospholipid antibodies: LA and ACA (IgG and IgM)	Yes	Yes	Yes	Weak evidence
aβ2GPI	Possible (not statistically significant)	Possible	No data	No data

Time interval after pregnancy (loss) is not known.

Confirmation of the positive test results after 12 weeks is necessary

Immunological conditions

Recommendation (updated in 2022)

Human Leukocyte Antigen (HLA) determination in women with RPL is not recommended in clinical practice. Only HLA class II determination (HLA-DRB1*15:01, HLA-DRB1*07 and HLA-DQB1*05:01/05:02) could be considered in Scandinavian women with secondary RPL after the birth of a boy, for explanatory and prognostic purposes.	Conditional ⊕⊕■■

Justification

	Association	Contributing factor	Prognosis	Treatment
HLA-compatibility	Controversial evidence	NA	No prognostic potential	NA
HLA class II: HLA-DR and HLA-DQ (maternal)	Strong, but only shown in Scandinavian women	YES, especially for secondary RPL after first born boy	Negative impact on future live birth	None available
HLA-G	Significant but weak	No data	No data	NA
KIR and HLA-C	Controversial evidence	No data	No data	NA

Immunological conditions

Recommendation

Measurement of anti-HY antibodies in women with RPL is not recommended in clinical practice.	Conditional ⊕⊕■■

Justification

	Association	Contributing factor	Prognosis	Treatment
Anti-HY immunity	Moderate (Only shown in Scandinavian women)	YES, especially for secondary RPL after first born boy	Negative impact on future live birth*	None available

** Prognostic impact is stronger for women with secondary RPL with a first-born boy and HLA class II alleles predisposing to anti-HY immunity*

Consider offering HLA-DRB1 typing to women with RPL after a birth of a boy for clarification of the pathogenesis and assessment of prognosis. However, the testing will provide no change in treatment offers.

Immunological conditions

Recommendations

Cytokine testing should not be used in women with RPL in clinical practice.	Strong	⊕⊕■■

Cytokine polymorphisms should not be tested in women with RPL.	Strong	⊕⊕⊕■

Justification

	Association	Contributing factor	Prognosis	Treatment
Cytokines	Yes	Unclear	Unknown	NA
Polymorphisms in cytokine genes	No association	NA	NA	NA

The role of cytokines in RPL is complex -> their functions change according to production of blood lymphocytes.
Plasma cytokine concentrations may be completely different from that in the uterus.
The studies have shown an association between TNF-α and RPL, the relevance of routine testing is unclear.

Immunological conditions

Recommendation

Antinuclear antibodies (ANA) testing could be considered for explanatory purposes.	Conditional ⊕⊕■■■

Justification

	Association	Contributing factor	Prognosis	Treatment
ANA antibodies	Yes	Probably not – no documentation	Unclear	NA

Whether ANA positivity can identify a subset of women with RPL that responds beneficially to various forms of immunotherapy is unknown.

Immunological conditions

Recommendation

There is insufficient evidence to recommend NK cell testing of either peripheral blood or endometrial tissue in women with RPL.	Strong ⊕■■■

Justification

	Association	Contributing factor	Prognosis	Treatment
NK in Peripheral blood: numbers	Weak	No	Unclear – No	No
NK cell cytotoxicity in peripheral blood	Unclear	/	No	No
NK in endometrium / uterine	Weak	/	Unclear	No

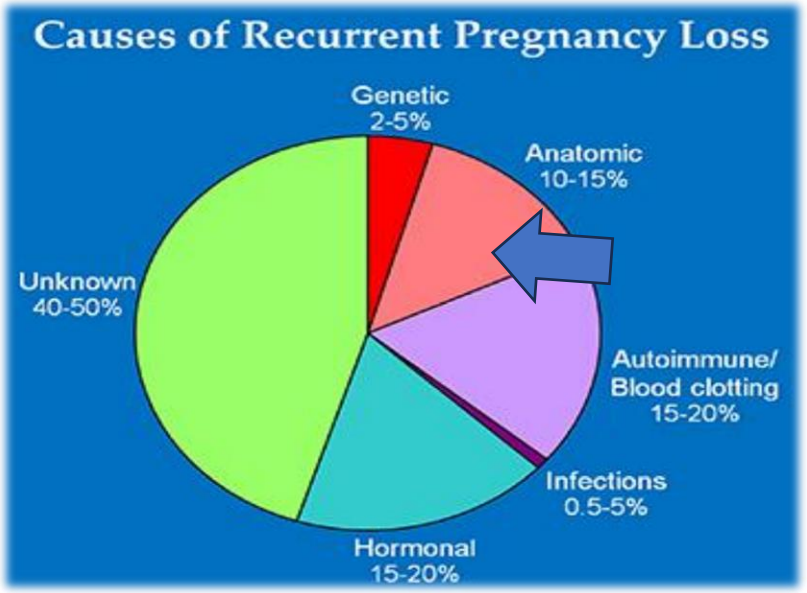
There seems to be a weak association of serum and endometrial NK with RPL, but NK cell testing cannot be used to select women with RPL for immunological treatments.

Lack of consensus about ranges of normal values and lack of standardization in the measurement of NK cells.

Other Immunological conditions

- Coeliac serum markers - tissue transglutaminase (tTG IgA + IgG) have been described in women with RPL in single study.
- Testing for celiac disease serum markers is not indicated in women with RPL in absence of symptoms of celiac disease.
- Anti-sperm antibodies have been associated with higher risk of RPL but the evidence is inconsistent and testing is not recommended.

Anatomic factors (10-15%)



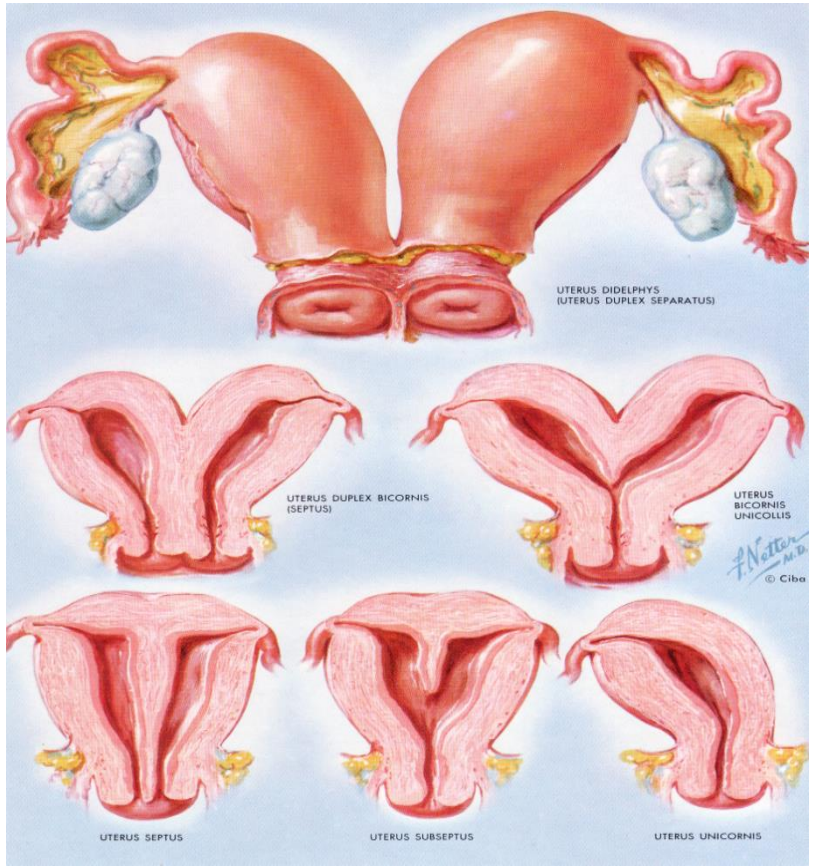
- Uterine
  - Inherited (Mullerian abnormalities):
    - Septate uterus
    - Bicornuate uterus
    - Unicornuate uterus
    - Uterus didelphis
  - Acquired:
    - Uterine adhesions (Asherman's syndrome)
    - Fibroids (submucous)
    - Endometrial polyps
    - Adenomyosis
- Hydrosalpinx
- Cervical incompetence – 2nd Trimester RPL
  - Inherited: Mullerian anomalies, DES exposure
  - Acquired: post conization/ post LLETZ

Congenital Uterine Anomalies

Incidence:

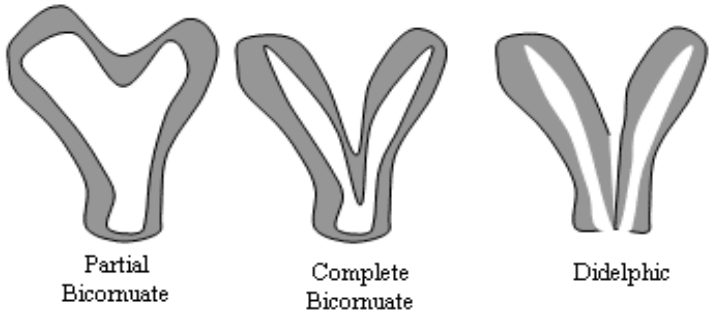
- **5%** in unselected population
- **8%** in infertile women
- **13%** in women with history of miscarriage

- Associated with increased miscarriage rates and preterm labor
- Diagnosis with 3D-US, Sonohysterography, HyCoSy (hystero-salpingo contrast sonography) or MRI
- Hysteroscopy + Laparoscopy – gold standard, invasive



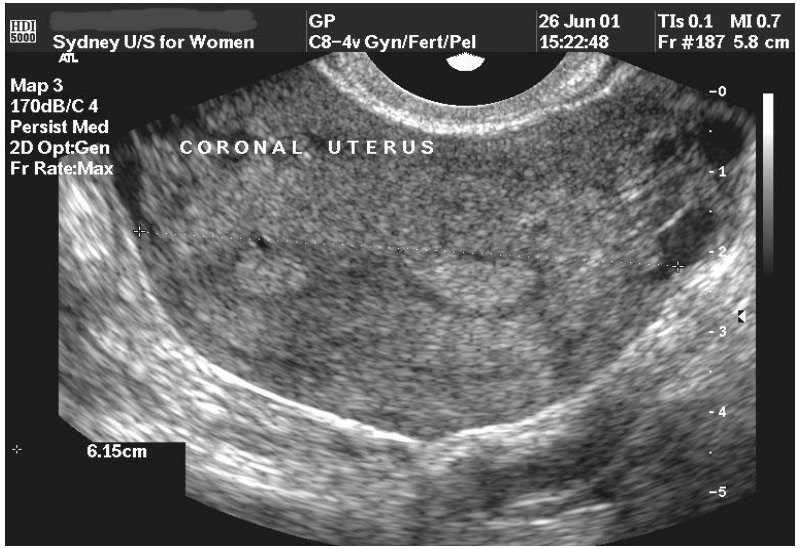
Chan Y et al., Reproductive outcomes in women with congenital uterine anomalies: a systematic review. Ultrasound Obstet Gynecol 2011; 38: 371-382
Ashton et al., 1988; Raga et al., 1997; Salim et al., 2003, Tulppala et al., 1993; Romer et al., 1994; Valli et al., 2001

Uterine Anomalies – Reproductive Outcomes

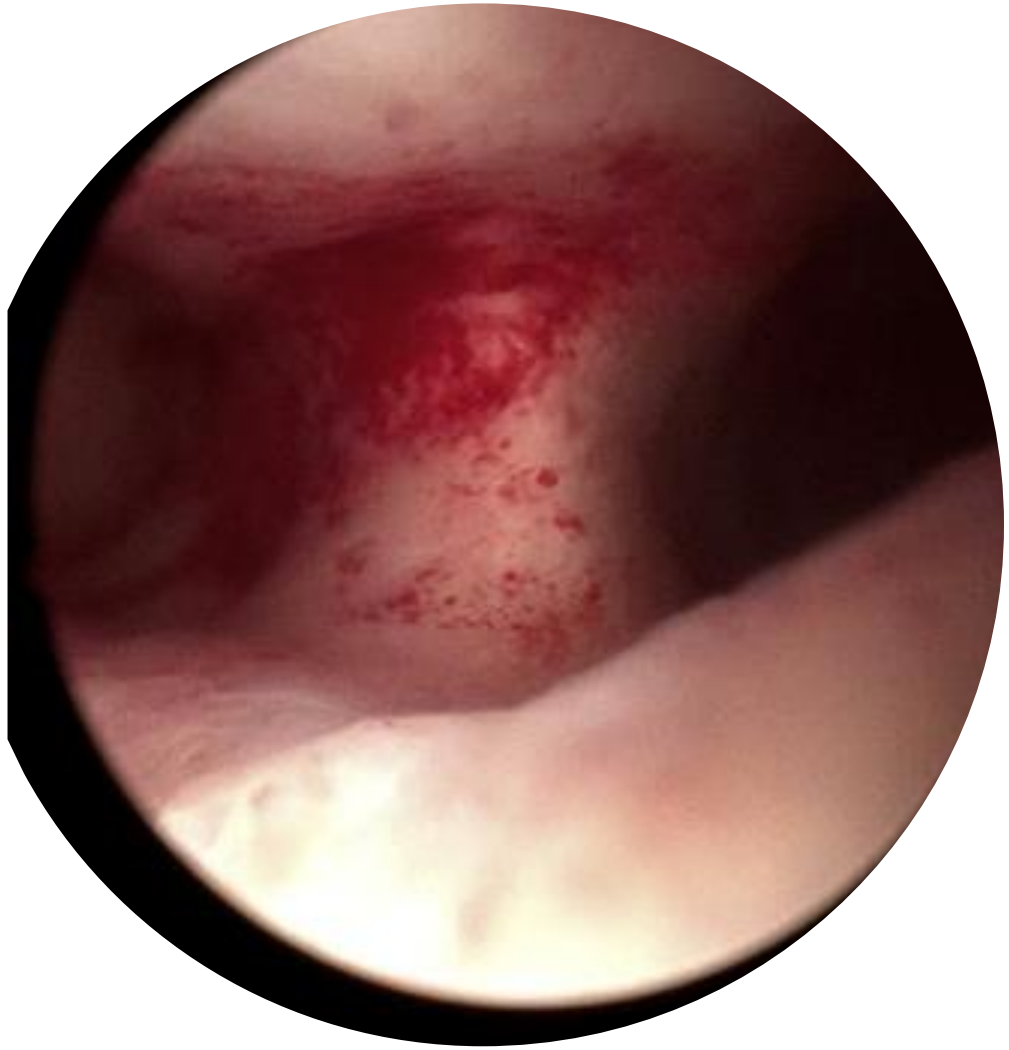


	n *of pregnancies*	*SAB* (n)
Historical controls	—	10%–15%[10]
Unicornuate uterus	393	34.4% (135)
Didelphic uterus	86	20.9% (18)
Bicornuate uterus	56	25.0% (14)
Uterine septum	1459	75.7% (1105/1459)

JWH 13(1) 33 2004



Uterine Septum



- Nonrandomized prospective trials have shown septate uteri to be associated with 67% chance of miscarriage and 47% lower fecundity (relative to post-transection) *Ghi T et al., The pregnancy outcome in women with incidental diagnosis of septate uterus at first trimester scan. Hum Reprod. 2012; 27: 2671-2675; Mollo A et al., Hysteroscopic resection of the septum improves the pregnancy rate of women with unexplained infertility: a prospective controlled trial. Fertil Steril 2009; 91: 2628-2631*

- ASRM Committee guidelines state that it may be reasonable to perform septal incision if septum is > 1.5 cm *Practice Committee of the American Society for Reproductive Medicine. Uterine septum. Fertil Steril 2016; 106: 530-540*

- In contrast, guidance on RPL from the European Society of Human Reproduction and Embryology (ESHRE), the National Institute for Health and Care Excellence (NICE) and the Royal College of Obstetricians and Gynaecologists (RCOG) do not support septum resection *RCOG, 2011; NICE, 2015; ESHRE, 2018*

Human Reproduction, Vol.36, No.5, pp. 1260–1267, 2021
Advance Access Publication on April 1, 2021 doi:10.1093/humrep/deab037

human reproduction

ORIGINAL ARTICLE *Gynaecology*

Septum resection versus expectant management in women with a septate uterus: an international multicentre open-label randomized controlled trial

J.F.W. Rikken[1,*], C.R. Kowalik[1], M.H. Emanuel[2], M.Y. Bongers[3], T. Spinder[4], F.W. Jansen[5], A.G.M.G.J. Mulders[6], R. Padmehr[7], T.J. Clark[8], H.A. van Vliet[9], M.D. Stephenson[10], F. van der Veen[1], B.W.J. Mol[11], M. van Wely[1], and M. Goddijn[1,*]

The TRUST (The Randomised Uterine Septum Trial)

The TRUST (The Randomised Uterine Septum Trial)

STUDY QUESTION: Does septum resection improve reproductive outcomes in women with a septate uterus?

SUMMARY ANSWER: Hysteroscopic septum resection does not improve reproductive outcomes in women with a septate uterus.

WHAT IS KNOWN ALREADY: A septate uterus is a congenital uterine anomaly. Women with a septate uterus are at increased risk of subfertility, pregnancy loss and preterm birth. Hysteroscopic resection of a septum may improve the chance of a live birth in affected women, but this has never been evaluated in randomized clinical trials. We assessed whether septum resection improves reproductive outcomes in women with a septate uterus, wanting to become pregnant.

STUDY DESIGN, SIZE, DURATION: We performed an international, multicentre, open-label, randomized controlled trial in 10 centres in The Netherlands, UK, USA and Iran between October 2010 and September 2018.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women with a septate uterus and a history of subfertility, pregnancy loss or preterm birth were randomly allocated to septum resection or expectant management. The primary outcome was conception leading to live birth within 12 months after randomization, defined as the birth of a living foetus beyond 24 weeks of gestational age. We analysed the data on an intention-to-treat basis and calculated relative risks with 95% CI.

MAIN RESULTS AND THE ROLE OF CHANCE: We randomly assigned 80 women with a septate uterus to septum resection (n = 40) or expectant management (n = 40). We excluded one woman who underwent septum resection from the intention-to-treat analysis, because she withdrew informed consent for the study shortly after randomization. Live birth occurred in 12 of 39 women allocated to septum resection (31%) and in 14 of 40 women allocated to expectant management (35%) (relative risk (RR) 0.88 (95% CI 0.47 to 1.65)). There was one uterine perforation which occurred during surgery (1/39 = 2.6%).

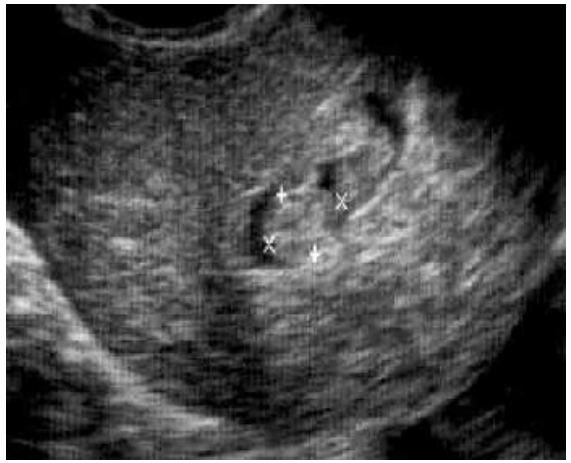
LIMITATIONS, REASONS FOR CAUTION: Although this was a major international trial, the sample size was still limited and recruitment took a long period. Since surgical techniques did not fundamentally change over time, we consider the latter of limited clinical significance.

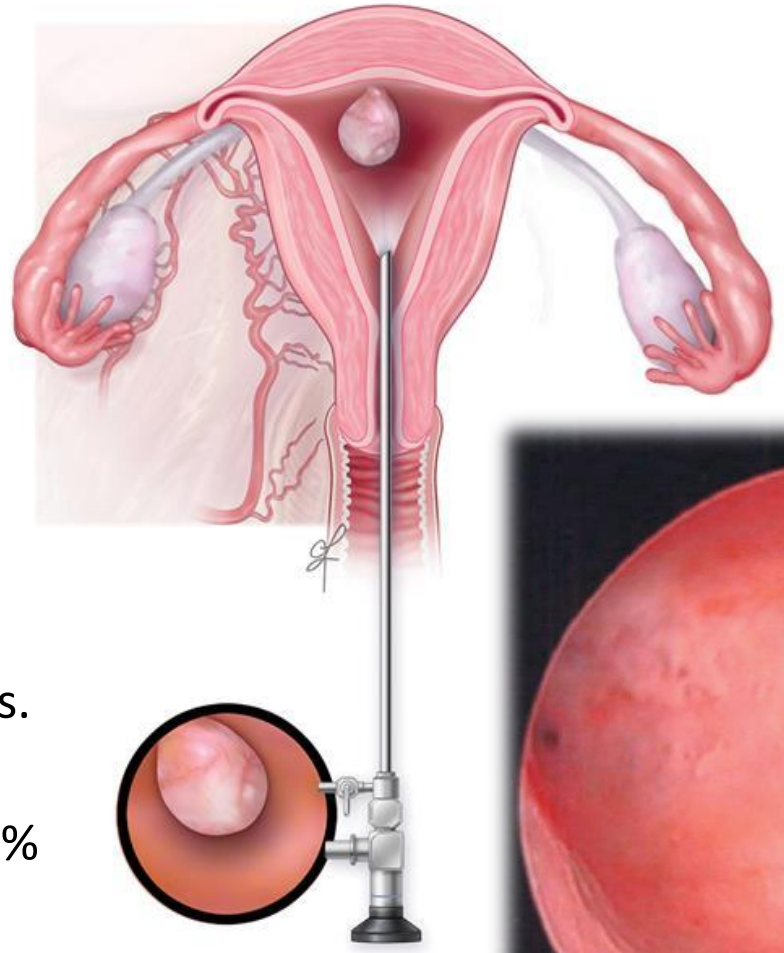
WIDER IMPLICATIONS OF THE FINDINGS: The trial generated high-level evidence in addition to evidence from a recently published large cohort study. Both studies unequivocally do not reveal any improvements in reproductive outcomes, thereby questioning any rationale behind surgery.

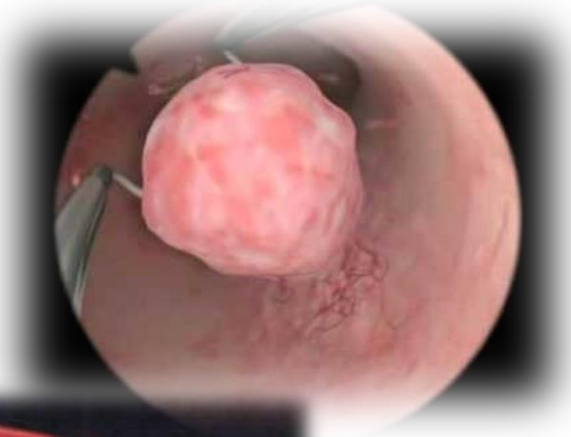
STUDY FUNDING/COMPETING INTEREST(S): There was no study funding. M.H.E. reports a patent on a surgical endoscopic

Pregnancy rates double after hysteroscopic resection of uterine polyps

Pérez-Medina T et al., Endometrial polyps and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. Hum Reprod. 2005; 20: 1632-1635

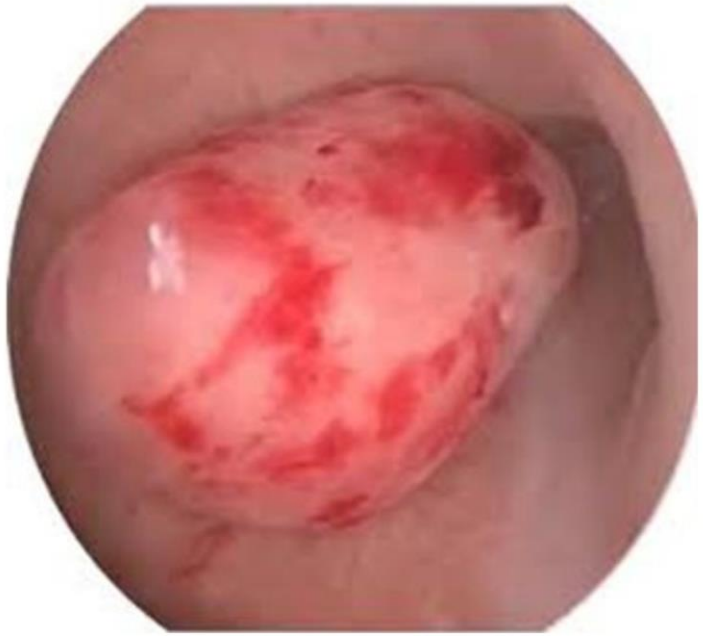


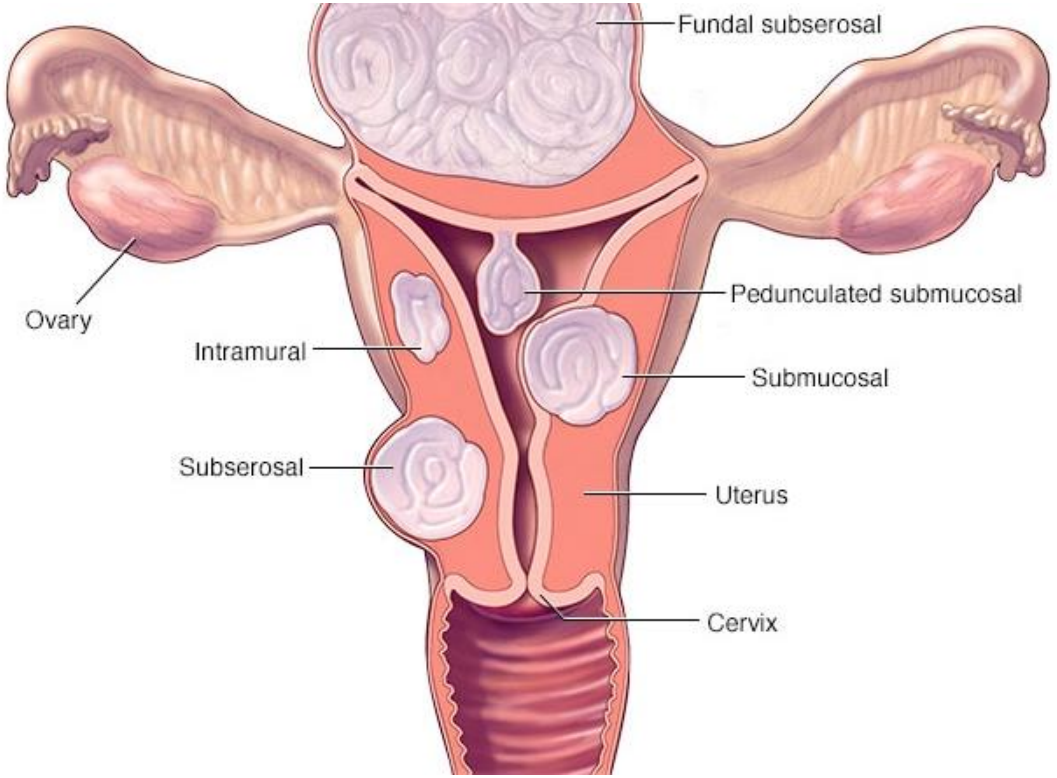




- RCT – 215 women before IUI, randomly allocated to hysteroscopic polypectomy vs. hysteroscopy + polyp biopsy
- Clinical pregnancy rate was 51.4% vs 25.4% over 4 cycles IUI
- 2/3 of conceptions occurred spontaneously within 3 months postop
- Polyp size did not matter

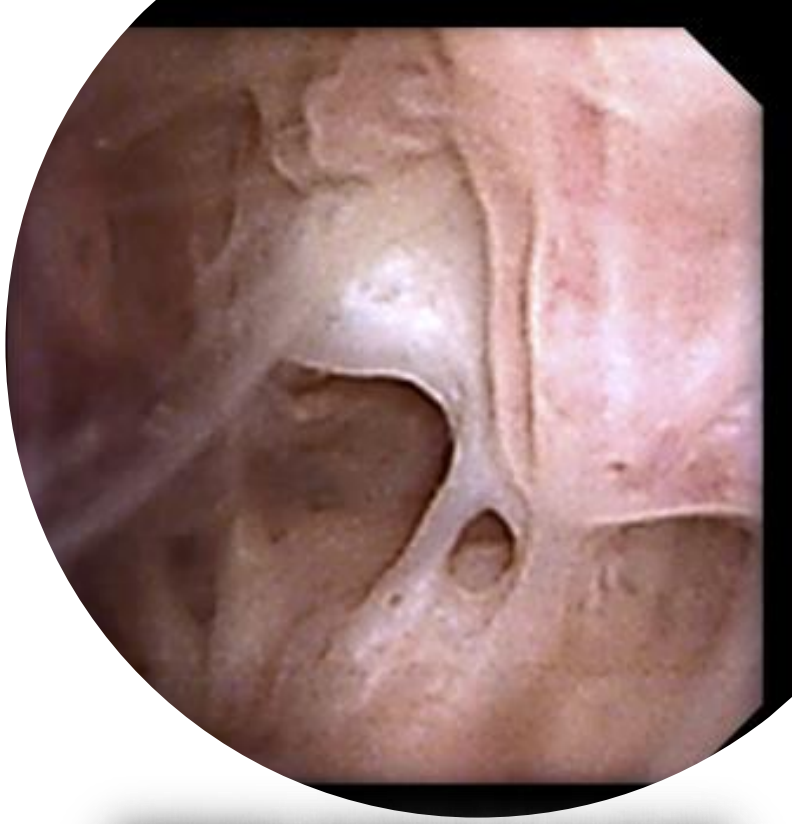
Uterine Fibroids
Submucous



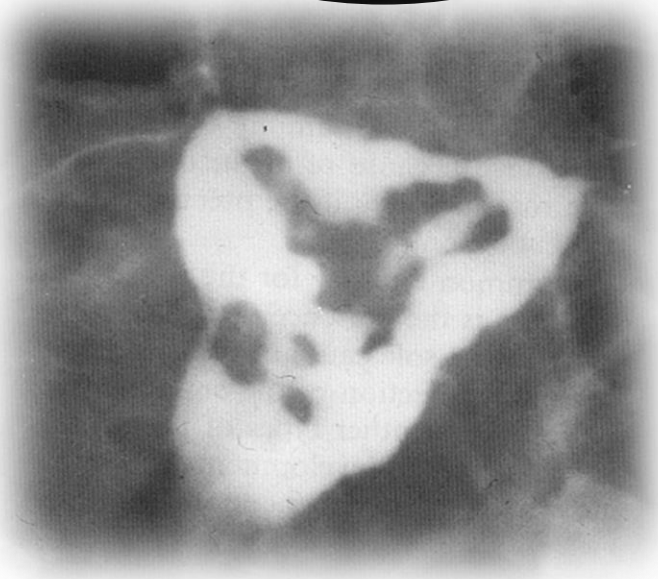


Hysteroscopic myomectomy increased pregnancy rates from 27% to 43% and decreased miscarriage rates by more than 10% ***Casini ML et al.,*** *Effects of the position of fibroids on fertility. GynecolEndocrinol 2006; 22: 106-109*

Intrauterine adhesions (Asherman's syndrome)



- Leads to abnormal placentation, recurrent miscarriage, and preterm labor
- Women with intrauterine adhesions and secondary infertility or recurrent pregnancy loss showed fecundity of 48% after hysteroscopic adhesiolysis
- The same study showed lower miscarriage rate (42.8% from 86.5%) post surgery

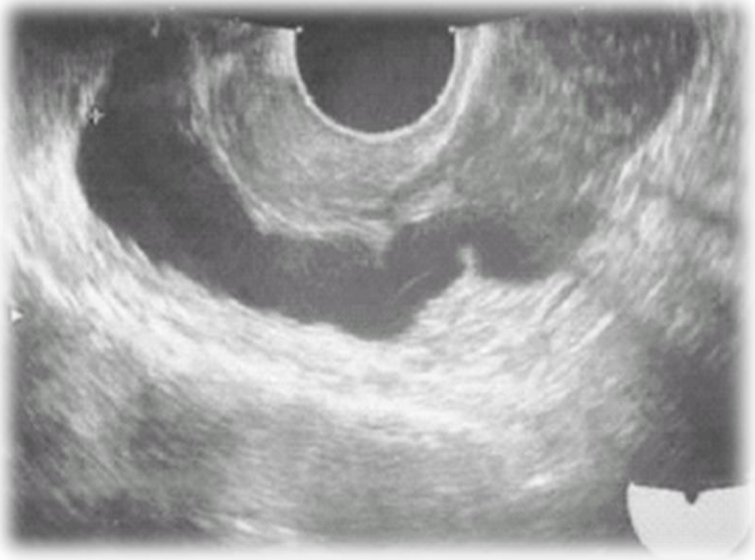


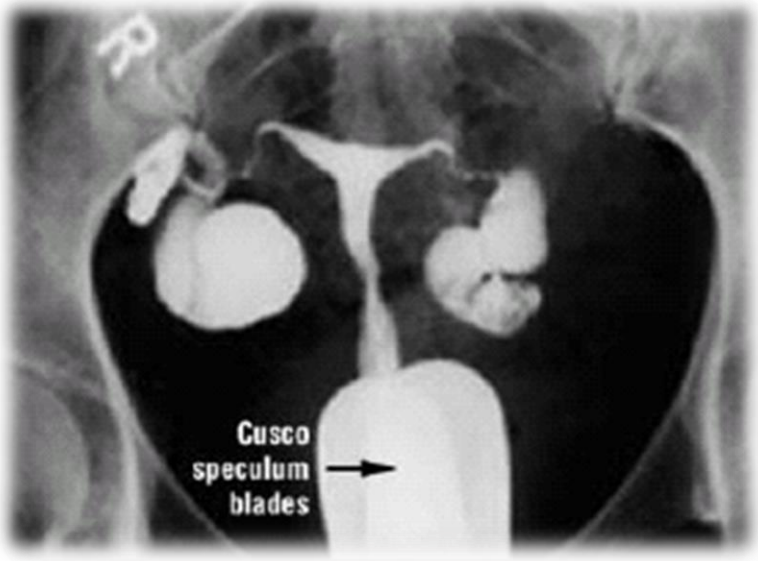
Goldenberg M et al., *Reproductive outcome following hysteroscopic management of intrauterine septum and adhesions.Hum Reprod 1995; 10: 2663-2665*

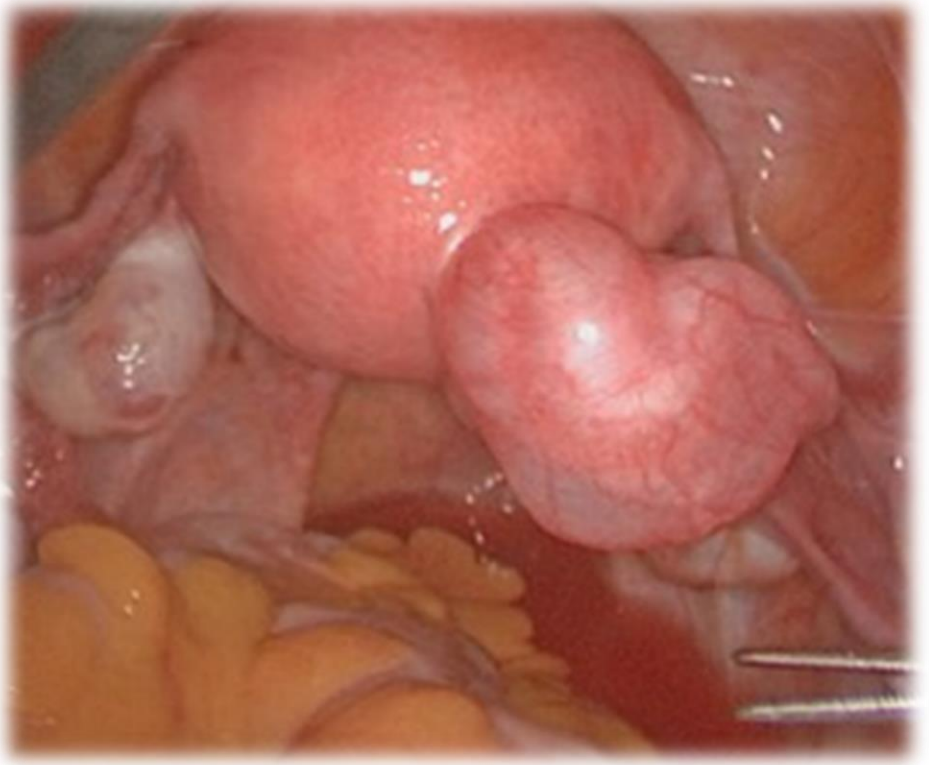
Robinson J et al., *Poostoperative adhesiolysis therapy for intrauterine adhesions (Asherman's syndrome).Fertil Steril 2008; 90: 409-414*

Hydrosalpinx

- Two meta-analyses**: Chance for pregnancy is ½, Risk of pregnancy loss x 2** *Zeyneloglu et al., 1998; Camus et al., 1999*
- Laparoscopic salpingectomy:
  - Lower concentrations of integrins, restored after removal *Dicker et al., 1991; Marcus and Edwards, 1994; Loh et al., 1999*
  - ↑ pregnancy rate x 1.75 & live birth rate x 2.13 overall ***Johnson et al.,*** *2002*
  - ↑ live birth rates x 2 (visible on u/s) & x3.5 (bilateral) ***Strandell et al.,*** *1999*







Anatomical factors

Recommendations (updated 2022)

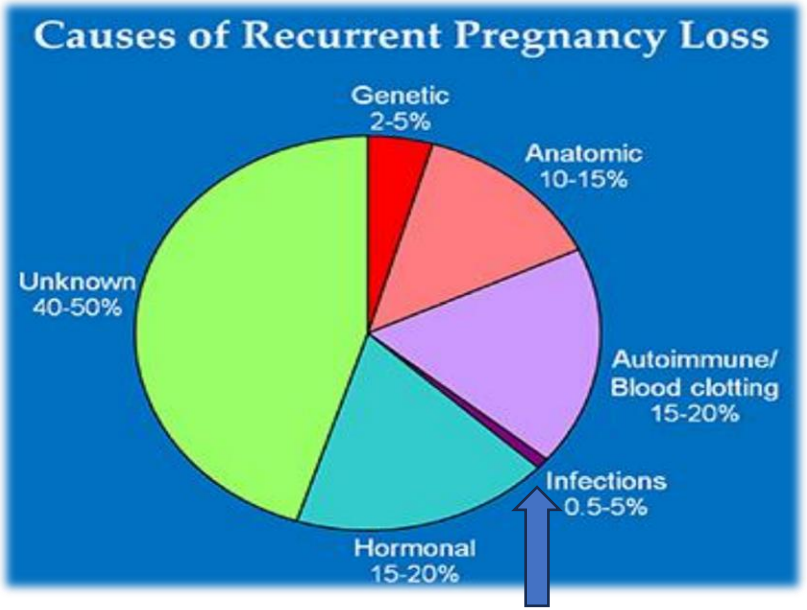
All women with RPL should have an assessment of the uterine anatomy.	Strong	⊕⊕■■
The preferred technique to evaluate the uterus is transvaginal 3D US, which has a high sensitivity and specificity, and can distinguish between septate uterus and bicorporeal uterus (former AFS bicornuate uterus) with normal cervix.	Conditional	⊕⊕■■
Sonohysterography (SHG) is more accurate than HSG in diagnosing uterine malformations. It can be used to evaluate uterine morphology when 3D US is not available, or when tubal patency has to be investigated.	Conditional	⊕⊕■■
If a Müllerian uterine malformation is diagnosed, further investigations (including investigation of the kidneys and urinary tract) should be considered.	Conditional	⊕⊕■■
MRI is not recommended as first line option for the assessment of uterine malformations in women with RPL but can be used where 3D US is not available.	Conditional	⊕⊕■■
All women with RPL could have 2D ultrasound to rule out adenomyosis.	Conditional	⊕⊕■■

Infections (0.5-5%)

- Vaginal cultures:
  - Ureaplasma urealiticum
  - Mycoplasma hominis
  - Chlamydia
- Serology
  - Listeria monocytogenes
  - Toxoplasma gondii
  - Rubella
  - CMV
  - HSV

Mainly in sporadic miscarriages, not in RPL

No recommendation for routine testing

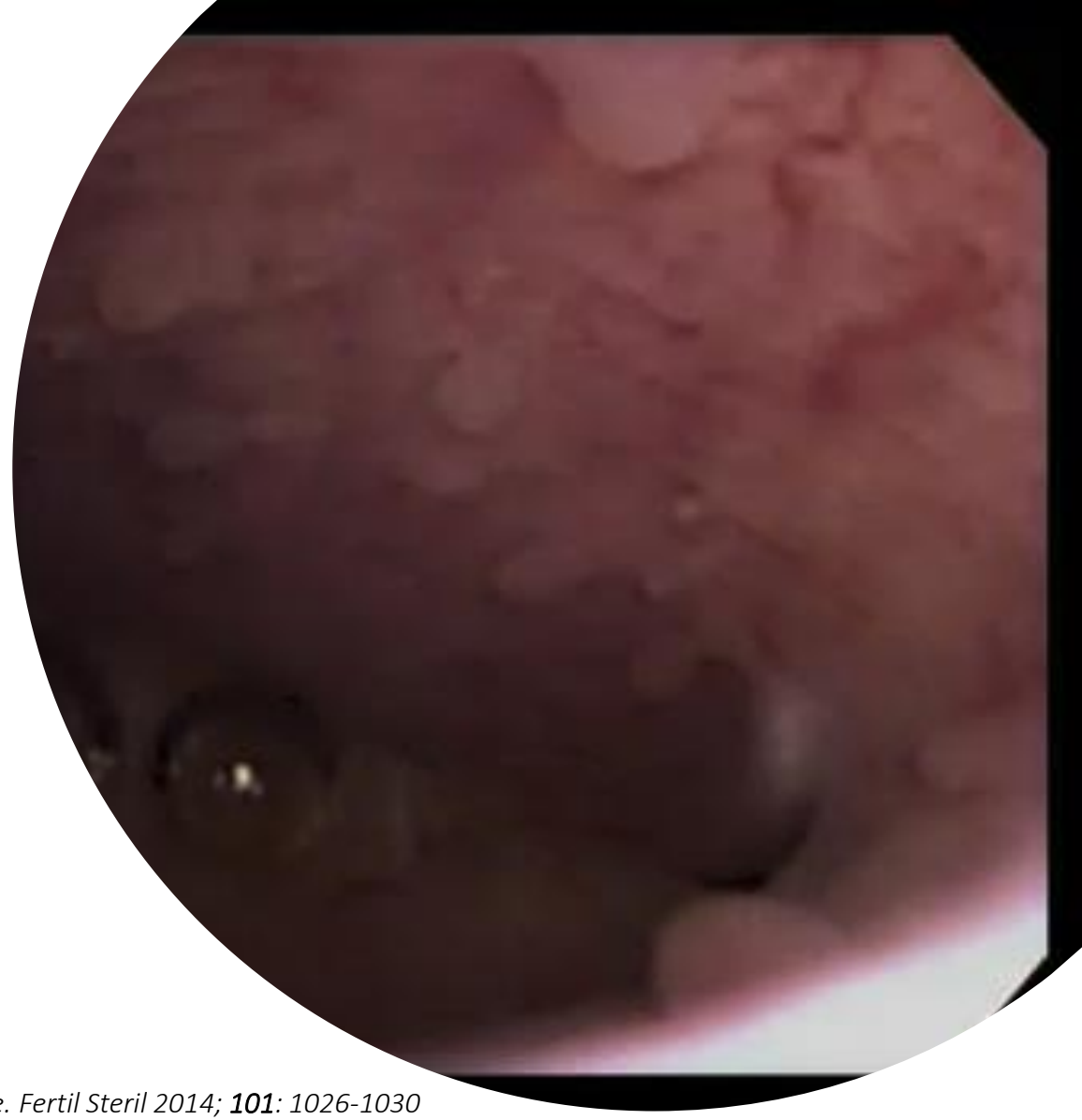


- Chronic endometritis

Infections

Chronic endometritis

- Can cause delayed endometrial maturation, leading to asynchrony with implantation
- Incidence - 0.5% in women with RPL
- Observed in women with recurrent implantation failure
- Diagnosis: endometrial biopsy for plasma cells (CD 138) or culture & sensitivity (Pipelle or Hysteroscopy)
- Antibiotic therapy seems to restore normal fecundity in affected patients (Doxycycline for 2-3 weeks)

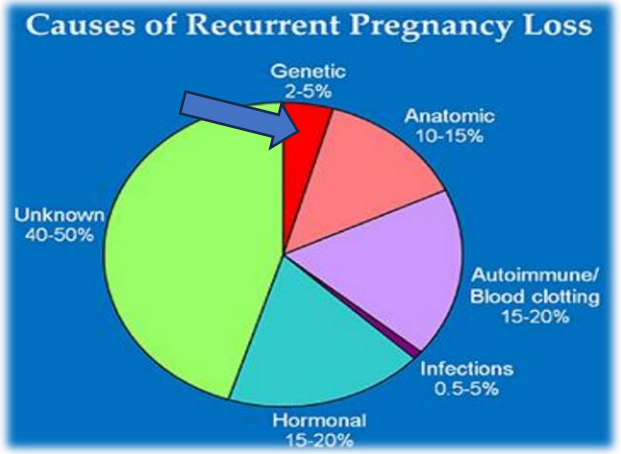


McQueen D et al., *Chronic endometritis in women with recurrent early pregnancy loss and/or fetal demise. Fertil Steril 2014;* ***101****: 1026-1030*

Zolghadri J et al., *The value of hysteroscopy in diagnosis of chronic endometritis in patients with unexplained recurrent spontaneous abortion.Eur J Obstet Gynecol 2011;* ***155****: 217-220*

Johnston-MacAnanny E et al., *Chronic endometritis is a frequent finding in women with recurrent implantation failure after in vitro fertilization. Fertil Steril 2010;* ***93****: 437-441*

Genetic disorders (2-5%)



70% of pregnancy loses < 12 weeks – due to chromosomal abnormalities

Aneuploidy (numerical chromosome errors) a cause of sporadic losses and RPL:

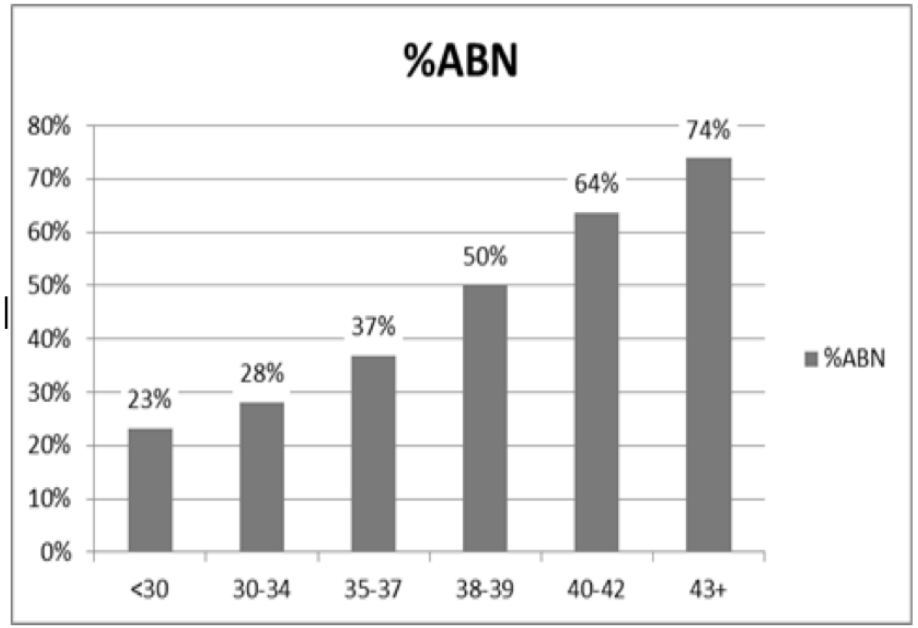
- Trisomy (52%)
- Polyploidy (21%)
- Monosomy X (13%)

- Increase with advancing maternal age
- Diagnosed on analysis of pregnancy tissue (POC)
- Prognosis is unclear (may not reoccur)

Structural chromosomal abnormalities in 6 - 8%

- Translocations
- Deletions
- Inversions

PGS and Aneuploidy



Stephenson et al., *Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case-control study. Hum Reprod. 2002;**17**:446–451.*

Genetic disorders

Parental karyotype abnormality in 1.9 – 3.5% couples

- The subsequent miscarriage rate is higher, and the live birth rate was lower in carrier couples, although the cumulative live birth rate was 64%

- Parental karyotyping can be recommended based on genetic history:
  - previous birth of a child with congenital abnormalities
  - offspring with unbalanced chromosome abnormalities in the family
  - detection of a translocation in the pregnancy tissue

- For other couples, the benefit of the test is limited as the chances of finding an abnormality are very low:
  - If female age > 39 y.o., less than three pregnancy losses and a negative family history -> the chance of being a carrier of a translocation is very low

Franssen, et al., *2005,* ***Franssen, et al.,*** *2006,* ***Stephenson and Sierra,*** *2006,* ***Sugiura-Ogasawara et al.,*** *2004,*

Genetic disorders

Recommendation

Genetic analysis of pregnancy tissue following pregnancy loss is not routinely recommended but it could be performed for explanatory purposes.	Conditional ⊕⊕■■

For genetic analysis of the pregnancy tissue following pregnancy loss, array-CGH is recommended based on a reduced maternal contamination effect.	Strong ⊕⊕■■

Justification

	Association	Contributing factor	Prognosis	Treatment
Karyotyping of the pregnancy tissue following pregnancy loss	Yes	Yes	No	No

Recommendations

Parental karyotyping could be carried out after individual assessment of risk for diagnostic purposes.	Conditional ⊕⊕■■

Justification

	Association	Contributing factor	Prognosis	Treatment
Parental genetic testing	Yes	Yes[1]	Yes[2]	PGT, adoption, gamete donation or other alternatives

[1] For couples with a parental chromosome abnormality, about one third of pregnancy losses are caused by parental chromosome abnormality; the other losses are aneuploidies, unexplained or a contribution of another underlying factor might exist.

[2] Increased chance of a subsequent pregnancy loss in case of carrier status; Negligible chance of a live born child with an unbalanced chromosome abnormality for the whole RPL population

Sperm DNA damage

- **Oxidative damages**
  - Excessive ROS
  - Deficient anti-oxidants
- **Susceptibility**
  - Sperm defects – loss of tight packaging of the DNA
- **Poor outcomes -**
  - Inadequate oocyte repairing capability
- **Associated with advanced paternal age**
- **Caused by unhealthy lifestyles**
  - Smoking, obesity and excessive exercise

de Ligny, et al., *2022,* ***Sharma et al.,*** *2013,* ***Wright et al.,*** *2014*

> Treatment options

- Lower ROS exposures
- Antioxidants
- NSAIDS
- Shorten sperm transit time (frequent ejaculations)
- Obtain sperm before damage – testicular sperm
- Lifestyle changes
- ICS –> if fertility treatments

Efficient treatment of infertility due to sperm DNA damage by ICSI with testicular spermatozoa

Human Reproduction Vol.20, No.1 pp. 226–230, 2005

Ermanno Greco[1], Filomena Scarselli[1], Marcello Iacobelli[1], Laura Rienzi[1], Filippo Ubaldi[1],

ICSI in cases of sperm DNA damage: beneficial effect of oral antioxidant treatment

Human Reproduction Vol.20, No.9 pp. 2590–2594, 2005

Ermanno Greco[1], Stefania Romano[1], Marcello Iacobelli[1], Susanna Ferrero[1], Elena Baroni[1], Maria Giulia Minasi[1], Filippo Ubaldi[1], Laura Rienzi[1] and Jan Tesarik[2,3]

Human Reproduction Vol.23, No.12 pp. 2663–2668, 2008
Advance Access publication on August 29, 2008
doi:10.1093/humrep/den321

Sperm DNA damage is associated with an increased risk of pregnancy loss after IVF and ICSI: systematic review and meta-analysis

Armand Zini[1,4], Jason M. Boman[1], Eric Belzile[2] and Antonio Ciampi[2,3]

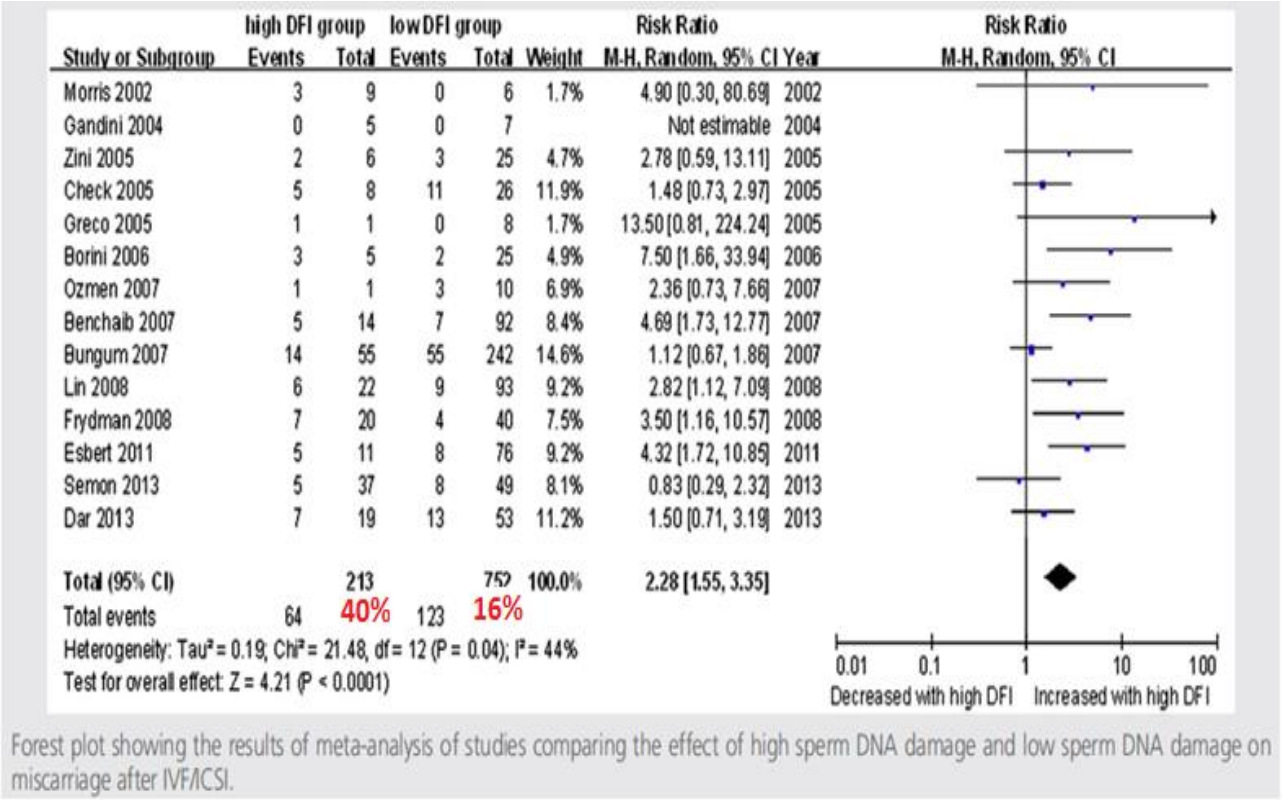
[1]*Division of Urology, Department of Surgery, St Mary's Hospital Center, Mary's Hospital, 3830 Lacombe Avenue, Montreal, Quebec, Canada H3T 1M5;* [2]*Department of Clinical Epidemiology and Community Studies, St. Mary's Hospital Center, Mary's Hospital, 3830 Lacombe Avenue, Montreal, Quebec, Canada H3T 1M5;* [3]*Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada*

[4]Correspondence address. Fax: +1-514-734-2718; E-mail: ziniarmand@yahoo.com

BACKGROUND: Sperm DNA damage is common amongst infertile men and may adversely impact natural reproduction, IUI-assisted reproduction and to a lesser degree IVF pregnancy. The aim of this study was to examine the influence of sperm DNA damage on the risk of spontaneous pregnancy loss after IVF and ICSI. METHODS: We conducted a systematic review and meta-analysis of studies on sperm DNA damage and pregnancy loss after an IVF and/or ICSI pregnancy. RESULTS: Two by two tables were constructed and odds ratios (ORs) were derived from 11 estimates of pregnancy loss (five IVF and six ICSI studies from seven reports). These 11 studies involved 1549 cycles of treatment (808 IVF and 741 ICSI cycles) with 640 pregnancies (345 IVF and 295 ICSI) and 122 pregnancy losses. The combined OR of 2.48 (95% CI 1.52, 4.04, $P < 0.0001$) indicates that sperm DNA damage is predictive of pregnancy loss after IVF and ICSI. CONCLUSIONS: In conclusion, sperm DNA damage is associated with a significantly increased risk of pregnancy loss after IVF and ICSI. These data provide a clinical indication for the evaluation of sperm DNA damage prior to IVF or ICSI and a rationale for further investigating the association between sperm DNA damage and pregnancy loss.

Sperm DNA damages – ART miscarriages

Whether sperm deoxyribonucleic acid fragmentation has an effect on pregnancy and miscarriage after in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis



Study or Subgroup	high DFI group Events	Total	low DFI group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Morris 2002	3	9	0	6	1.7%	4.90 [0.30, 80.69]	2002
Gandini 2004	0	5	0	7		Not estimable	2004
Zini 2005	2	6	3	25	4.7%	2.78 [0.59, 13.11]	2005
Check 2005	5	8	11	26	11.9%	1.48 [0.73, 2.97]	2005
Greco 2005	1	1	0	8	1.7%	13.50 [0.81, 224.24]	2005
Borini 2006	3	5	2	25	4.9%	7.50 [1.66, 33.94]	2006
Ozmen 2007	1	1	3	10	6.9%	2.36 [0.73, 7.66]	2007
Benchaib 2007	5	14	7	92	8.4%	4.69 [1.73, 12.77]	2007
Bungum 2007	14	55	55	242	14.6%	1.12 [0.67, 1.86]	2007
Lin 2008	6	22	9	93	9.2%	2.82 [1.12, 7.09]	2008
Frydman 2008	7	20	4	40	7.5%	3.50 [1.16, 10.57]	2008
Esbert 2011	5	11	8	76	9.2%	4.32 [1.72, 10.85]	2011
Semon 2013	5	37	8	49	8.1%	0.83 [0.29, 2.32]	2013
Dar 2013	7	19	13	53	11.2%	1.50 [0.71, 3.19]	2013
Total (95% CI)		213		752	100.0%	2.28 [1.55, 3.35]	
Total events	64	40%	123	16%			

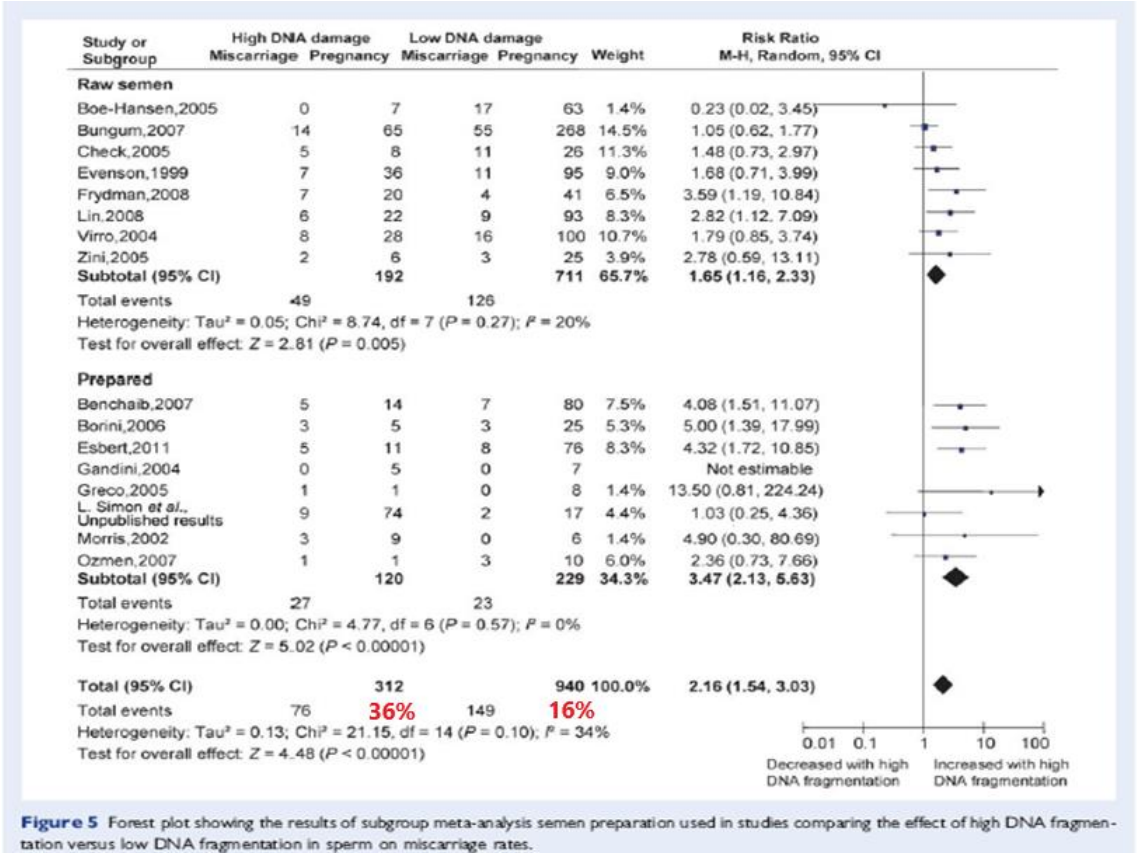
Heterogeneity: Tau² = 0.19; Chi² = 21.48, df = 12 (P = 0.04); I² = 44%
Test for overall effect: Z = 4.21 (P < 0.0001)

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Decreased with high DFI | Increased with high DFI

Forest plot showing the results of meta-analysis of studies comparing the effect of high sperm DNA damage and low sperm DNA damage on miscarriage after IVF/ICSI.

Fertility and Sterility® Vol. 102, No. 4, October 2014

The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis



Study or Subgroup	High DNA damage Miscarriage	Pregnancy	Low DNA damage Miscarriage	Pregnancy	Weight	Risk Ratio M-H, Random, 95% CI
Raw semen						
Boe-Hansen,2005	0	7	17	63	1.4%	0.23 (0.02, 3.45)
Bungum,2007	14	65	55	268	14.5%	1.05 (0.62, 1.77)
Check,2005	5	8	11	26	11.3%	1.48 (0.73, 2.97)
Evenson,1999	7	36	11	95	9.0%	1.68 (0.71, 3.99)
Frydman,2008	7	20	4	41	6.5%	3.59 (1.19, 10.84)
Lin,2008	6	22	9	93	8.3%	2.82 (1.12, 7.09)
Virro,2004	8	28	16	100	10.7%	1.79 (0.85, 3.74)
Zini,2005	2	6	3	25	3.9%	2.78 (0.59, 13.11)
Subtotal (95% CI)		192		711	65.7%	1.65 (1.16, 2.33)
Total events	49		126			
Heterogeneity: Tau² = 0.05; Chi² = 8.74, df = 7 (P = 0.27); P = 20%						
Test for overall effect: Z = 2.81 (P = 0.005)						
Prepared						
Benchaib,2007	5	14	7	80	7.5%	4.08 (1.51, 11.07)
Borini,2006	3	5	3	25	5.3%	5.00 (1.39, 17.99)
Esbert,2011	5	11	8	76	8.3%	4.32 (1.72, 10.85)
Gandini,2004	0	5	0	7		Not estimable
Greco,2005	1	1	0	8	1.4%	13.50 (0.81, 224.24)
L. Simon *et al.*, Unpublished results	9	74	2	17	4.4%	1.03 (0.25, 4.36)
Morris,2002	3	9	0	6	1.4%	4.90 (0.30, 80.69)
Ozmen,2007	1	1	3	10	6.0%	2.36 (0.73, 7.66)
Subtotal (95% CI)		120		229	34.3%	3.47 (2.13, 5.63)
Total events	27		23			
Heterogeneity: Tau² = 0.00; Chi² = 4.77, df = 6 (P = 0.57); P = 0%						
Test for overall effect: Z = 5.02 (P < 0.00001)						
Total (95% CI)		312		940	100.0%	2.16 (1.54, 3.03)
Total events	76	36%	149	16%		
Heterogeneity: Tau² = 0.13; Chi² = 21.15, df = 14 (P = 0.10); I² = 34%						
Test for overall effect: Z = 4.48 (P < 0.00001)						

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Decreased with high DNA fragmentation | Increased with high DNA fragmentation

Figure 5 Forest plot showing the results of subgroup meta-analysis semen preparation used in studies comparing the effect of high DNA fragmentation versus low DNA fragmentation in sperm on miscarriage rates.

Lynne Robinson[1,*], Ioannis D. Gallos[1,2], Sarah J. Conner[1,2], Madhurima Rajkhowa[1], David Miller[3], Sheena Lewis[4], Jackson Kirkman-Brown[1,2], and Arri Coomarasamy[1,2]

Human Reproduction, Vol.27, No.10 pp. 2908–2917, 2012

Recommendation

Genetic analysis of pregnancy tissue following pregnancy loss is not routinely recommended but it could be performed for explanatory purposes.	Conditional	⊕⊕■■

For genetic analysis of the pregnancy tissue following pregnancy loss, array-CGH is recommended based on a reduced maternal contamination effect.	Strong	⊕⊕■■

Justification

	Association	Contributing factor	Prognosis	Treatment
Karyotyping of the pregnancy tissue following pregnancy loss	Yes	Yes	No	No

Recommendations

Parental karyotyping could be carried out after individual assessment of risk for diagnostic purposes.	Conditional	⊕⊕■■

Justification

	Association	Contributing factor	Prognosis	Treatment
Parental genetic testing	Yes	Yes[1]	Yes[2]	PGT, adoption, gamete donation or other alternatives

[1] For couples with a parental chromosome abnormality, about one third of pregnancy losses are caused by parental chromosome abnormality; the other losses are aneuploidies, unexplained or a contribution of another underlying factor might exist.

[2] Increased chance of a subsequent pregnancy loss in case of carrier status; Negligible chance of a live born child with an unbalanced chromosome abnormality for the whole RPL population

Recommendations

All couples with results of an abnormal fetal or parental karyotype should receive genetic counselling.	GPP
All couples with results of an abnormal fetal or parental karyotype may be informed about the possible treatment options available including their advantages and disadvantages.	GPP

Recommendations (updated 2022)

In couples with RPL, it is recommended to assess lifestyle factors in the male partner (paternal age, smoking, alcohol consumption, exercise pattern, and body weight).	Strong	⊕⊕■■
Assessing sperm DNA fragmentation in couples with RPL could be considered for diagnostic purposes.	Conditional	⊕⊕⊕■

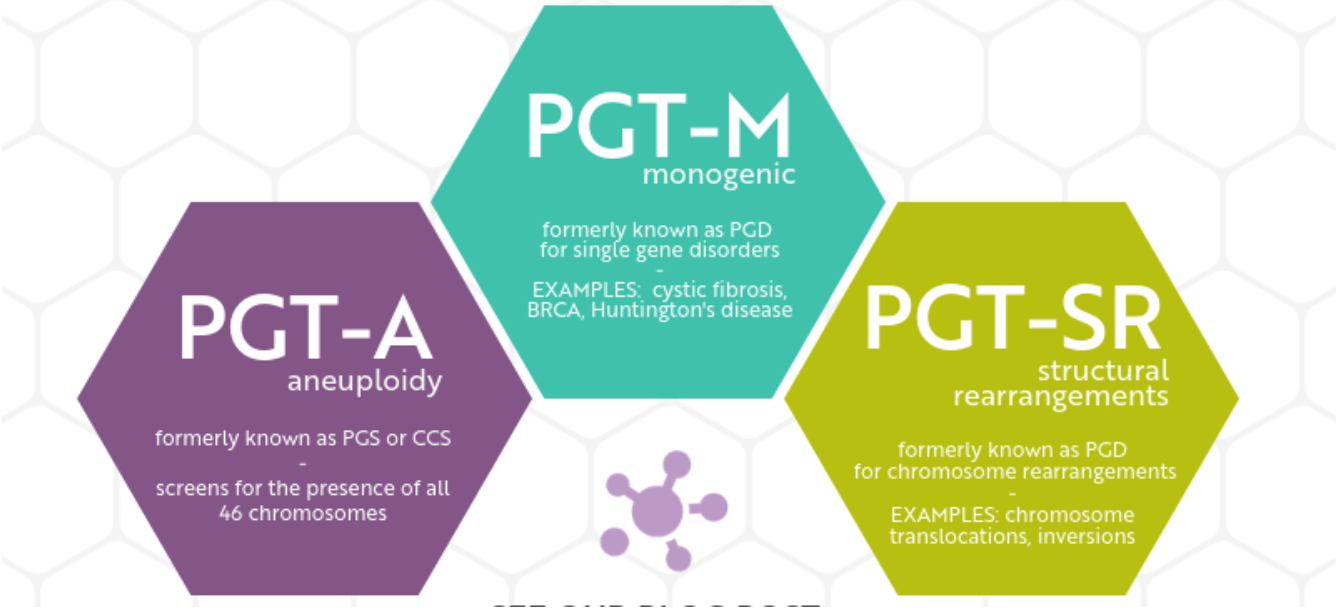
Justification

	Association	Contributing factor	Prognosis	Treatment
Sperm DNA damage	Yes	Yes	requires further clarification	Changing lifestyle and for couples having ICSI, the use of hyaluronan selection looks promising. Further studies are needed to confirm this benefit.

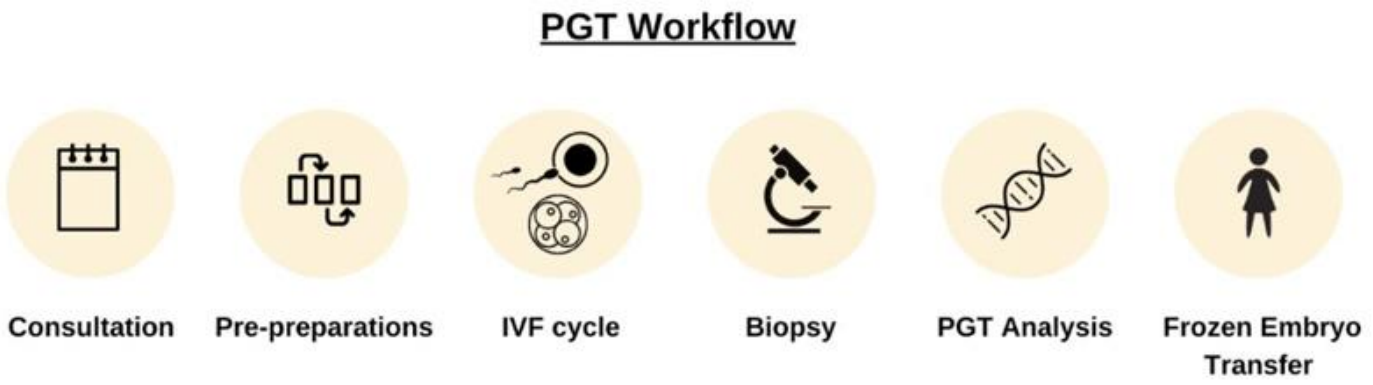
Several assays have been described to measure sperm DNA damage.
It has not been established which test is most informative and most reliable.

Preimplantation Genetic Testing

There are 3 types of preimplantation genetic testing (PGT).
All require in vitro fertilization (IVF).

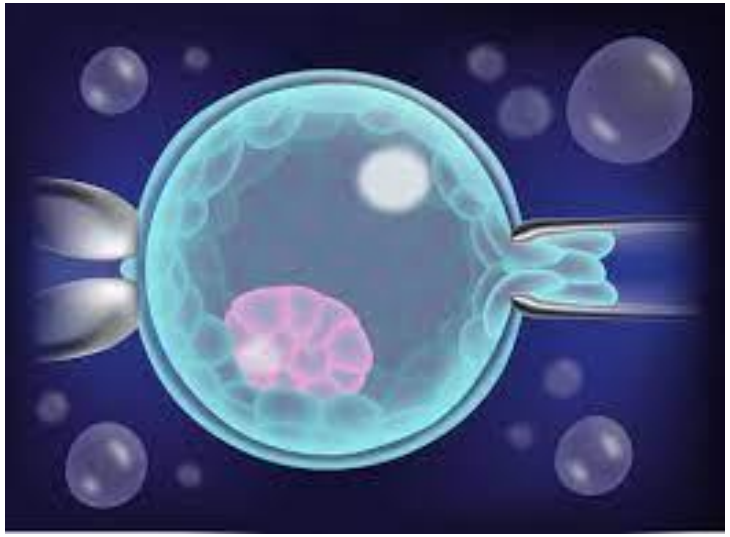


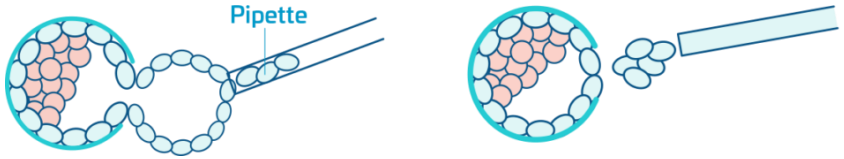
Not a cure but improves embryo selection



Day 5 *(200-300 cells in total)* **biopsy**

2-9 cells from trophectoderm





Treatments

Treatment plan, supportive care, psychological support

- Time for questions, information, repetition and discussion
- Good listening: to the facts and the feelings
- Respect: for the patient, her partner (male or female), and the pregnancies (or babies) lost
- Clear and sensitive language: explaining terminology, avoiding insensitive terms (recurrent abortion, products of conception, blighted ovum, incompetent cervix, pregnancy failure), and mirroring the patient's preferred terms (baby, fetus, pregnancy etc.)
- Honesty: about processes, likely outcomes, prognoses; avoid false reassurance
- Shared planning: a partnership approach, enabling some element of control
- Supportive care in the next pregnancy: access to the team (actual, by phone or online), additional/early scans if wanted
- Kindness: concern, empathy, compassion as appropriate for that patient

Treatments

- **Proven benefit:** hydrosalpinx removal, resection of polyps and SM fibroids, thyroid and DM control, PGT-SR/M (if parental chromosomal abnormality)
- **Likely benefit:** chronic endometritis, vaginal progesterone, lifestyle changes, weight loss, PGT-A
- **Empirical**
  - **Heparin?**
  - **Aspirin?**
  - **Prednisolone?**
  - **Intralipid?**
  - **PRP (Platelet Rich Plasma)?**

Treatments

Recommendation

For women with hereditary thrombophilia and a history of RPL, we suggest not to use antithrombotic prophylaxis unless in the context of research, or if indicated for VTE prevention.	Conditional	⊕⊕■■

Recommendations

For women who fulfil the laboratory criteria of APS and a history of three or more pregnancy losses, we suggest administration with low-dose aspirin (75 to 100 mg/day) starting before conception, and a prophylactic dose heparin (UFH or LMWH) starting at date of a positive pregnancy test, over no treatment.	Conditional	⊕■■■
The GDG suggests offering anticoagulant treatment for women with two pregnancy losses and APS, only in the context of clinical research.	GPP	
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.	Strong	⊕⊕⊕■

No immunological biomarker, except for high-titer antiphospholipid antibodies can be used for selecting couples with RPL for specific treatments.

Treatments

Recommendations (updated 2022)

Overt hypothyroidism arising before conception or during early gestation should be treated with levothyroxine in women with RPL.	Strong	⊕⊕■■
There is conflicting evidence regarding treatment effect of levothyroxine for women with subclinical hypothyroidism and RPL. Treatment of women with SCH may reduce the risk of miscarriage, but the potential benefit of treatment should be balanced against the risks.	Conditional	⊕⊕■■
If women with subclinical hypothyroidism and RPL are pregnant again, TSH level should be checked in early gestation (7-9 weeks gestational age), and hypothyroidism should be treated with levothyroxine.	GPP	
If women with thyroid autoimmunity and RPL are pregnant again, TSH level should be checked in early gestation (7-9 weeks gestational age), and hypothyroidism should be treated with levothyroxine.	GPP	
Euthyroid women with thyroid antibodies and RPL should not be treated with levothyroxine.	Strong	⊕⊕⊕■

Recommendations

There is insufficient evidence to recommend the use of progesterone to improve live birth rate in women with RPL and luteal phase insufficiency.	Conditional	⊕⊕⊕■
There is insufficient evidence to recommend the use of hCG to improve live birth rate in women with RPL and luteal phase insufficiency.	Conditional	⊕⊕■■
There is insufficient evidence to recommend metformin supplementation in pregnancy to prevent PL in women with RPL and glucose metabolism defects.	Conditional	⊕■■■
Preconception counselling in women with RPL could include the general advice to consider prophylactic vitamin D supplementation.	GPP	
Couples with RPL should be informed that smoking, alcohol consumption, obesity and excessive exercise could have a negative impact on their chances of a live birth, and therefore cessation of smoking, a normal body weight, limited alcohol consumption and a normal exercise pattern is recommended.	GPP	

Summary

- Recurrent miscarriages occur more frequently than expected by chance
- Only small percentage of women have a treatable underlying cause
- The chance of an ongoing pregnancy decreases with age and number of previous miscarriages
- Need to balance between evidence-based approach and large gap in evidence:
  - Patients at high risk of having a miscarriage may not need absolute scientific certainty to choose to have a treatment
  - If informed about the uncertainty around treatment effects and available safety data, the patients can decide for themselves the right course of action
- IVF without PGT has the same chances for miscarriage as those who fall pregnant naturally
- PGT-A can improve the chances of an ongoing pregnancy and reduce the miscarriage rates by selecting euploid embryos for transfer

Recourses

European Society of **Human Reproduction and Embryology**

Login

Patient version 2023

Version 2017

Download the full guideline

Guideline on the management of recurrent pregnancy loss

Issued: 1 February 2023

RPL

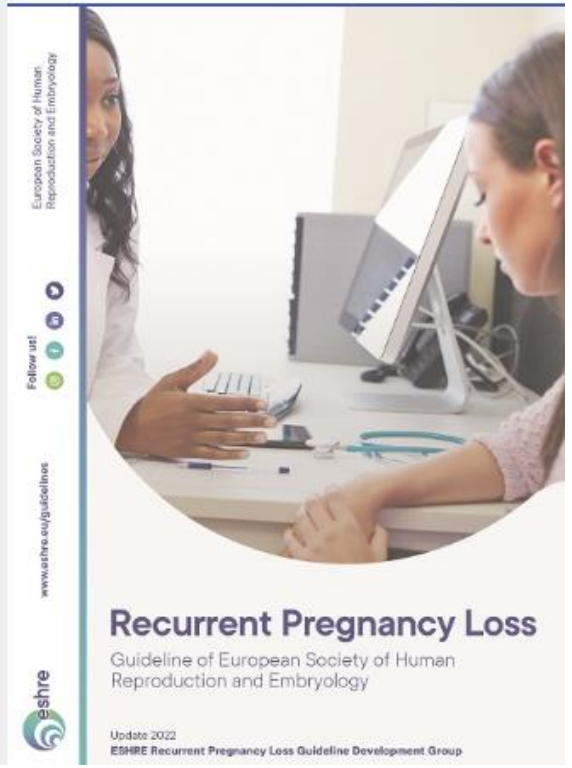
The updated guideline is now available. The guideline development group hope to ensure this guideline remains relevant and useful to clinical practice, with this updated edition reflecting the latest published studies in the field.

We believe this update will provide even more value to members who rely on the 2017 version for the care and management of women with recurrent pregnancy loss.

Please do not hesitate to provide feedback or ask questions by sending an e-mail to guidelines@eshre.eu.

Guideline development group

Read the guideline



Thank you

RPL may be due to:

👉Genetic abnormalities

account for 60% of 1st trimester losses
balanced translocation (2-5%)

👉Uterine abnormalities

present in ~13% of RPL patients

👉Medical conditions

untreated thyroid or diabetes,
antiphospholipid syndrome(~15%)

👉Lifestyle factors

Smoking increases risk of pregnancy loss

👉Unexplained

no cause found in up to 50%

FertilitySpace

Andrew, 32 years old and Kate, 30 years old

WHY???

What are our chance for healthy pregnancy?

What tests do we need to complete?

What treatments can help?

Trying to conceive for 3 years (from age 29/27)

Four pregnancy losses since started trying

Emotionally exhausted and anxious

Not sure if can carry pregnancy

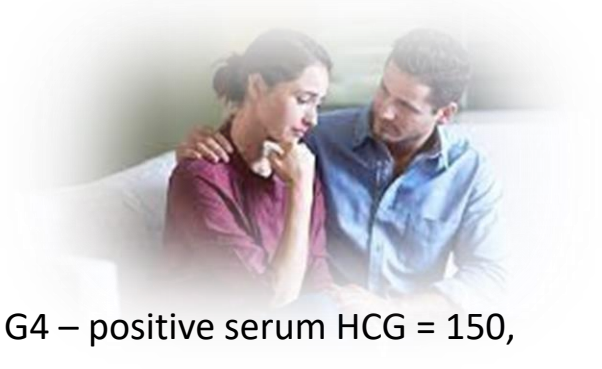
Keen to get some answers

Andrew and Kate

Kate 30 yo

- G4P0
- CIN III LLETZ, recent smear normal
- Ex-smoker (5-10/d for years till after 1st miscarriage 3 yrs ago)
- Family: Nil sig
- U/S: normal uterus, ovaries features of PCO
- Sono hysterogram: no evidence of endometrial abnormality
- Karyotype 46 XX
- Vaginal & Cervical Swab – no pathogens isolated
- Endometrial biopsy – no endometritis or hyperplasia

Andrew and Kate



Kate 30 yo

- History:
  - Gyn hx: G4P0:
    - G1 – no FHR on US 8/40, G2 – only positive urine test, G3 – empty sac on US 7/40 weeks, G4 – positive serum HCG = 150, then bleeding and negative HCG
    - regular cycle K5/28; CIN III LLETZ, recent CST normal
  - Medical hx: Nil sig
  - Family Hx: Nil sig
  - Ex-smoker (5-10/d for years till after 1st miscarriage 3 yrs ago); ETOH - nil
- Investigations:
  - Day 2 blood test: FSH 6, LH 3.4, Testosterone 1.5, SHBG 29, FAI 5.2%, TSH 1.5, Prolactin 155
  - Fasting glucose 4.9, insulin 10
  - Luteal blood test: P4 30 (day 21), 39 (day 23)
  - Karyotype 46 XX
  - Thrombophilia screenings –ve
  - Vaginal & Cervical Swab – no pathogens isolated
  - Luteal endometrial biopsy – no endometritis /hyperplasia; in phase adequate luteal effect, uNK cells – normal profile
  - U/S: normal uterus, ovaries features of PCO
  - Sono hysterogram: no evidence of endometrial abnormality

Andrew and Kate

Andrew 32 yo

- History:
  - Medical hx: Nil sig
  - Family Hx: Nil sig
  - Non-smoker; ETOH – nil; BMI = 28
- Investigations:
  - Karyotype: 46 XY
  - Fasting Homocysteine: 10 (6-15), Fasting Glu 4.5
  - Sperm DNA Fragmentation Index (DFI) 15%

- Do this couple meet criteria of RPL?
- Additional history?
- Considerations for further investigations/ treatments?
- Additional tests?
- Referrals?
- Next management step?

Considerations for Investigation and Treatment

- Woman's age
- Ovarian reserve
  - AMH
  - Antral follicle count
- Length of time to conception
- Desired family size
- Is she losing normal or abnormal embryos?
- If karyotype is *normal*, consider investigations
- If karyotype is *abnormal*, options are:
  - Keep trying
  - IVF with PGT-A