

# Research recommendations for Recurrent Pregnancy Loss (RPL)

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From the literature and discussion of the available evidence, several topics were identified for which evidence is inconsistent, insufficient or non-existing. For the benefit of couples with RPL, the GDG recommends that future research, where possible in well-designed RCTs, should focus on these research gaps.

## Definition of RPL

- Perform epidemiological studies on the effect of various RPL definitions on diagnosis, prognosis, or treatment.

## Organization of Care

- Study the (emotional) impact of RPL on men.
- Develop a prognostic model to provide an individually based live birth prognosis.
- Develop E-health tools for support to couples with RPL and staff.

## Genetics

- Establish the value of using NGS for PGD-A in couples with RPL.
- The role of genetic analysis of pregnancy tissue needs to be clarified (prognostic modelling).

## Thrombophilia

- Study the effect of anticoagulant treatment for RPL women with hereditary thrombophilia
- With regard to RPL and APS:
  - Study clinical criteria for diagnosis and treatment of APS (e.g. female age, number of pregnancy losses, consecutive or non-consecutive losses).
  - Assess the effectiveness of heparin treatment from comparison with placebo/no treatment
  - Compare the efficacy and safety of LMWH versus UFH.
  - How should heparin be administered; start before conception (ante partum), start after fetal heartbeat, throughout whole pregnancy from positive pregnancy test, up to 36 weeks or later?
  - Evaluate the effect of hydroxychloroquine in couples with RPL. Hydroxychloroquine has been safely used in APS pregnancies and lupus pregnancies for preventing obstetric complications.

## Immunology

- Study the effect of moderate dosages of prednisolone in RPL (preferably in large controlled trials).
- Study the effect of IvIg treatment in women with secondary RPL.
- Study the effect of immunotherapy in subsets of women with RPL with specific HLA class II alleles (in RCTs)

### Metabolic factors

- Study the effect of Levothyroxine treatment in women with RPL and identified thyroid auto-immunity.
- Study the effect of Levothyroxine treatment in women with RPL and identified subclinical hypothyroidism.

### Uterine malformations

- Clarify the role of congenital uterine malformations in RPL and the associated live birth rates per type of congenital uterine abnormality (preferably in well-controlled prospective trials).
- Evaluate whether hysteroscopic septum resection has beneficial effects in women with RPL (increasing live birth rates, and decreasing miscarriage rates, without doing harm).

### Male factor

- In general, there is very little evidence on the role of the man in RPL couples.
- Study the impact of unhealthy lifestyle (such as obesity, poor diet and smoking) on RPL through sperm DNA damage (preferably in prospective studies with appropriate controls, matched for age, fertility status and lifestyle).
- Study the mechanisms of sperm DNA damage.
- Study the effect of male lifestyle alterations with outcomes of both sperm DNA per se and RPL (in randomized controlled trials).
- Study the effect of antioxidant therapy for men on RPL; specifically to determine the best combinations and extent of dietary vitamin supplementation in the protection of sperm DNA from fragmentation.

### Female factor

- Study the effect of pre-conceptual weight loss on live birth rate using diet, exercise of therapeutic interventions.
- Define optimal endometrial characteristics for pregnancy; develop tests that detect women with sub-optimal endometrium and treatments to improve it.
- Further research is needed on the role of (chronic) endometritis in RPL, including prospective observational studies and randomized controlled trials.