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Review Article

Doing enough without doing everything: evidence-based management of recurrent first-trimester miscarriage in resource-limited settings

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ABSTRACT

Recurrent first-trimester miscarriage is a common but difficult problem in obstetric and gynaecological practice. The difficulty is greater in resource-limited settings, where genetic testing, specialised coagulation assays and advanced imaging may be unavailable or unaffordable. This narrative review examines a practical question: which investigations and treatments are sufficiently useful to justify their cost and burden in women with recurrent early pregnancy loss? A focused literature search of PubMed/MEDLINE, the Cochrane Library and major professional guidelines was updated to October 2026. The evidence supports a careful reproductive and medical history, assessment of maternal age and modifiable risk factors, evaluation of uterine anatomy, thyroid function testing and appropriately prioritised testing for antiphospholipid syndrome. Glycaemic assessment should be risk-directed. Genetic analysis of miscarriage tissue is informative when available, but routine inherited thrombophilia, natural-killer-cell, broad immunological and infection screening have limited first-line value. Folic acid remains appropriate preconception care but is not a specific treatment for recurrent miscarriage. Aspirin and heparin should principally be used for appropriately diagnosed antiphospholipid syndrome. Vaginal micronized progesterone has the clearest evidence in women with previous miscarriage who develop bleeding in a subsequent intrauterine pregnancy; evidence for routine progestogen use in otherwise unexplained recurrent miscarriage is weaker. Routine prednisolone is not supported. Resource limitation should therefore favour selective investigation, cause-directed treatment and structured early-pregnancy supportive care.

Keywords: Recurrent miscarriage, Recurrent pregnancy loss, First trimester, Resource-limited settings, Progesterone, Antiphospholipid syndrome

INTRODUCTION

Recurrent pregnancy loss (RPL) is a distressing reproductive problem in which the clinical task is often less straightforward than the patient expects. Current professional bodies do not use an identical definition. The American Society for Reproductive Medicine (ASRM), European Society of Human Reproduction and Embryology (ESHRE) and Society of Obstetricians and Gynaecologists of Canada (SOGC) recognise RPL after two pregnancy losses, whereas the Royal College of

Obstetricians and Gynaecologists (RCOG) retains three or more first-trimester miscarriages in its formal definition but allows earlier evaluation when the pattern suggests more than sporadic loss.¹⁻⁴

Repeated miscarriage has consequences beyond the loss itself. It is associated with substantial psychological morbidity and may also mark increased risk in subsequent pregnancies.⁵ A 2023 systematic review found higher rates of depression, anxiety and stress among women affected by RPL than among comparison groups, reinforcing the

need to regard counselling and continuity of care as part of treatment rather than as optional additions.⁶

The practical burden of RPL depends heavily on the setting in which care is delivered. In a Nigerian tertiary-centre study, 15.34% of the women studied met a two-loss definition compared with 5.29% when a three-loss definition was applied, illustrating how the chosen threshold can alter the number of women referred for investigation.⁷ An African scoping review published in 2025 identified restricted diagnostic capacity, cost and unequal access to specialist services as important barriers to RPL care in low and middle-income countries.⁸

The underlying causes are heterogeneous. A 2026 systematic review and meta-analysis found that unexplained RPL remained the largest aetiological category, accounting for about 37% of investigated cases, while acquired thrombophilia, endocrine and anatomical causes represented smaller proportions.⁹ This means that even extensive investigation does not always produce a diagnosis. In a resource-limited setting, the aim therefore cannot be to reproduce every investigation available in a specialist reproductive-medicine centre. The more useful question is whether a test is likely to identify a condition that changes treatment, prognosis or counselling. The same principle applies to treatment. Diagnostic uncertainty can encourage empirical combinations of aspirin, heparin, progesterone, dydrogesterone and corticosteroids. A subsequent live birth after such treatment does not, by itself, prove that the treatment was responsible. The purpose of this review is to identify a defensible minimum approach to recurrent first-trimester miscarriage that is clinically useful, affordable where possible and consistent with contemporary evidence.

REVIEW APPROACH

This article is a narrative review and did not involve collection of primary patient data. A focused literature search was conducted in PubMed/MEDLINE and the Cochrane Library and supplemented by current guidance from ASRM, ESHRE, RCOG, SOGC and NICE. The search was updated to 15 October 2026 using combinations of the terms “recurrent pregnancy loss”, “recurrent miscarriage”, “first trimester”, “antiphospholipid syndrome”, “thrombophilia”, “progesterone”, “dydrogesterone”, “aspirin”, “heparin”, “prednisolone” and “resource-limited” or “low-resource”. Recent guidelines, systematic reviews, meta-analyses and randomised trials were prioritised; older studies were retained when they remained clinically important. No formal meta-analysis was undertaken.

THE CLINICAL PROBLEM IN A RESOURCE-LIMITED SETTING

RPL is a clinical phenotype rather than a single disease. Two women with three first-trimester miscarriages may have very different explanations: repeated age-related

embryonic aneuploidy, a uterine abnormality, antiphospholipid syndrome (APS), an endocrine disorder, or no identifiable abnormality. This heterogeneity explains why a standard list of laboratory tests performs poorly when it is applied without reference to the history.

Genetic testing is a good example. Chromosomal abnormalities are common in first-trimester miscarriage, and meta-analysis confirms that abnormal fetal karyotypes remain frequent in products of conception from women with RPL.¹⁰ More recent work has shown that chromosomal microarray analysis of miscarriage tissue can substantially reduce the proportion of cases labelled “unexplained” when it is combined with a conventional RPL work-up.¹¹ However, this technology is not routinely available in many low-resource hospitals and may be beyond the financial reach of patients even when a referral laboratory exists. Assessment of uterine anatomy is more accessible and can identify clinically relevant congenital or acquired abnormalities. Congenital uterine anomalies are associated with a higher risk of miscarriage and other adverse reproductive outcomes.¹² Three-dimensional ultrasonography is preferred where available, but a good transvaginal ultrasound is a reasonable first step when advanced imaging is not readily accessible.

APS deserves particular attention because it is one of the few acquired conditions in RPL for which diagnosis directly changes treatment. Contemporary classification criteria incorporate clinical and laboratory domains, including lupus anticoagulant, anticardiolipin antibodies and anti-beta-2-glycoprotein-I antibodies.¹³ Classification criteria are not identical to clinical diagnostic rules, but they emphasise the importance of persistent, clinically meaningful antiphospholipid antibody positivity rather than an isolated test result. A further challenge is distinguishing investigations that are part of routine obstetric care from those that explain recurrent early miscarriage. ABO/Rh blood grouping and red-cell antibody screening remain important in pregnancy care, but they are not usually explanations for recurrent first-trimester loss. In contrast, uterine assessment, thyroid function and appropriately selected APS testing are more directly relevant to the RPL question.

A PRACTICAL MINIMUM EVALUATION

The first assessment should be clinical rather than laboratory based. The clinician should document the number and gestational age of previous losses, whether fetal cardiac activity had been demonstrated, previous live births, maternal age, menstrual and endocrine symptoms, previous uterine procedures, chronic disease, medications, personal or family thrombosis, autoimmune disease and relevant family history. BMI, smoking, alcohol intake and other modifiable factors should also be reviewed.

Uterine imaging should be included in the initial evaluation. Where resources are limited, transvaginal or pelvic ultrasound can be used as the first-line study, with

three-dimensional ultrasound, saline-infusion sonography or hysteroscopy reserved for abnormal or uncertain findings.^{3,4,12}

Thyroid-stimulating hormone (TSH) is a reasonable high-priority laboratory test because clinically significant thyroid dysfunction is treatable and the assay is widely available. Current guidelines differ on whether thyroid-peroxidase antibodies should be tested routinely, but in a constrained setting thyroid function itself has more immediate therapeutic relevance.^{1,3,4}

Glycaemic testing should be guided by risk rather than ordered automatically for every woman. HbA1c is useful in women with obesity, previous gestational diabetes, a strong family history of diabetes or other metabolic risk factors; fasting plasma glucose may be a pragmatic alternative where HbA1c is unavailable.^{1,4}

APS testing should be prioritised when the clinical pattern raises sufficient suspicion, particularly with repeated

unexplained losses, previous thrombosis, autoimmune disease, later fetal loss or severe placental-mediated complications. Where resources allow, broader screening after two recurrent losses is consistent with ESHRE and SOGC guidance.^{2,4}

Genetic testing of miscarriage tissue is valuable when available, but its absence should not prevent appropriate care. Parental karyotyping is better reserved for selected couples, for example when an unbalanced structural chromosomal abnormality has been identified, a family history is suggestive, or repeated losses remain unexplained and fetal tissue could not be tested.^{1,3,10,11}

By contrast, routine inherited-thrombophilia panels, MTHFR testing, natural-killer-cell assays, cytokine or HLA testing, broad immune panels and indiscriminate infection screening should not form part of a basic RPL package. Major guidelines consistently question their value in routine first-line investigation.¹⁻⁴

Table 1: Suggested investigation priorities in a resource-limited RPL service.

Assessment/investigation	Priority	Practical use
Detailed reproductive, medical and family history	Essential	Determines the probability of different causes and directs subsequent testing.
Maternal age, BMI and lifestyle assessment	Essential	Important for prognosis and modifiable risk.
Pelvic/transvaginal ultrasound	High priority	First-line assessment of uterine anatomy.
TSH	High priority	Identifies clinically important, treatable thyroid dysfunction.
Antiphospholipid antibody testing	High-value targeted test	Prioritise according to loss pattern, thrombosis/autoimmune history and available resources.
HbA1c or fasting plasma glucose	Risk-directed	Useful when diabetes or metabolic risk is present.
Genetic testing of miscarriage tissue	Valuable where available	May explain the loss and reduce unnecessary investigations.
Parental karyotype	Selective	Best used when fetal testing or family history suggests a structural chromosomal problem.
Prolactin	Symptom-directed	Consider with galactorrhoea, amenorrhoea or ovulatory disturbance.
Blood group/Rh and antibody screen	Routine obstetric care	Important for pregnancy care but not primary aetiological RPL tests.
Inherited thrombophilia, NK-cell, cytokine/HLA or routine TORCH panels	Not routine	Low clinical utility in otherwise unexplained first-trimester RPL.

TREATMENT IN THE NEXT PREGNANCY

Folic acid

Folic acid should be prescribed as part of routine preconception care because of its established role in preventing neural-tube defects.¹⁴ It is important to explain, however, that folic acid is not a specific treatment for

unexplained recurrent miscarriage. Its use is appropriate because the woman is planning pregnancy, not because it has been shown to prevent RPL.

Low-dose aspirin and heparin

Empirical aspirin is common in recurrent miscarriage because placental microthrombosis is biologically

plausible. The evidence does not support routine aspirin or heparin for otherwise unexplained RPL. Earlier Cochrane evidence found insufficient benefit in women without APS and the ALIFE2 randomised trial subsequently showed that low-molecular-weight heparin did not improve live birth even in women with recurrent loss and confirmed inherited thrombophilia.^{15,16} APS is different. In women with persistent antiphospholipid antibodies and recurrent pregnancy loss, evidence favours heparin combined with low-dose aspirin over aspirin alone, although the certainty of the evidence is not high.¹⁷ For a low-resource service, this is a useful example of why a relatively costly investigation may still represent good value: a confirmed diagnosis changes management.

Progesterone and dydrogesterone

The evidence for progesterone depends on the clinical situation. In the PROMISE trial, vaginal micronised progesterone started soon after a positive pregnancy test did not significantly improve live birth among women with unexplained recurrent miscarriage.¹⁸ By contrast, the PRISM trial of women with early-pregnancy bleeding identified benefit in the subgroup with previous miscarriage, with the greatest effect in women with several prior losses.¹⁹

NICE therefore recommends vaginal micronised progesterone 400 mg twice daily for women with an ultrasound-confirmed intrauterine pregnancy, vaginal bleeding and at least one previous miscarriage, continuing to 16 completed weeks if fetal cardiac activity is confirmed.²⁰ The 2025 Cochrane update also concluded that progestogens probably make little or no difference when used routinely to prevent miscarriage in women with unexplained recurrent miscarriage.²¹ These findings support targeted rather than automatic progesterone treatment after every positive pregnancy test.

Dydrogesterone remains relevant in countries where oral treatment is more readily available or acceptable. Older pooled evidence suggested possible benefit in recurrent miscarriage, but the quality of that evidence is weaker than the large modern trials of vaginal micronised progesterone.²² A 2024 systematic review found no clear additional risk of congenital anomalies after first-trimester dydrogesterone exposure, although safety evidence should not be interpreted as proof of efficacy.²³ Dydrogesterone can therefore be discussed as a pragmatic option when vaginal micronised progesterone is unavailable or unsuitable, but equivalence should not be assumed.

Prednisolone

Prednisolone has been used empirically on the assumption that immune dysregulation contributes to some unexplained miscarriages. Current ASRM and ESHRE guidance do not support routine immune testing or routine glucocorticoid treatment for unexplained RPL.^{1,2} In a resource-limited setting, inability to perform specialised immune assays should not itself become an indication for corticosteroid therapy. Prednisolone should be reserved for another recognised maternal indication or a properly governed research setting.

Treat conditions that are actually identified

Where investigation identifies a clinically important disorder, treatment should be directed at that condition. Overt thyroid disease and poor glycaemic control should be corrected; clinically important uterine pathology should be referred for appropriate assessment; and APS should be managed with an evidence-based antithrombotic regimen. This approach is more defensible than prescribing several agents simultaneously in the hope of covering multiple theoretical causes.

Table 2: Practical position on commonly used interventions.

Intervention	Practical position	Comment
Folic acid	Routine preconception/early-pregnancy care	Recommended for neural-tube-defect prevention; not a specific RPL treatment.
Low-dose aspirin alone	Not routine for unexplained RPL	Use should be linked to a recognised indication.
Aspirin plus heparin	Use for appropriately diagnosed obstetric APS	Diagnosis should precede treatment wherever feasible.
Heparin for unexplained RPL or inherited thrombophilia alone	Not routine	ALIFE2 did not show improved live birth in inherited thrombophilia.
Vaginal micronised progesterone	Targeted use	Best supported when early-pregnancy bleeding occurs in a woman with previous miscarriage.
Dydrogesterone	Selected pragmatic use	Oral option; evidence of efficacy is less robust than for the guideline-supported vaginal regimen.
Prednisolone	Not routine for unexplained RPL	Empirical immunosuppression is not supported by current guidelines.

Supportive care and early pregnancy follow-up

Avoiding unnecessary medication does not mean withholding care. RCOG and other contemporary reviews emphasise supportive follow-up, clear communication and ready access to early-pregnancy assessment.^{3,24} This is particularly important because recurrent loss carries a substantial psychological burden.^{5,6}

A practical low-resource plan is to review the woman before conception, correct identifiable medical problems, prescribe folic acid and agree on when she should return after a positive pregnancy test. Early review allows medication reconciliation, assessment of pain or bleeding and ultrasound at an appropriate gestational age to establish location and viability. Such a pathway can often be organised without expensive technology.

Women with unexplained RPL should also be given a realistic prognosis. The absence of a specific diagnosis does not imply that another miscarriage is inevitable. Reassurance is more useful when it is accompanied by a clear plan for early access, rather than by multiple prescriptions whose benefit is uncertain.

DISCUSSION

The main difficulty in resource-limited RPL care is deciding where limited diagnostic and therapeutic effort should be concentrated. International guidelines are helpful, but they are written for health systems with very different access to laboratory and imaging services. Applying them intelligently requires prioritisation rather than simple replication.

Accordingly, the proposed minimum evaluation is deliberately modest: careful history, assessment of maternal age and modifiable risks, uterine imaging, TSH, risk-directed glycaemic testing and appropriately prioritised APS testing. Genetic analysis of miscarriage tissue should be used when feasible because it can provide valuable explanatory information, but lack of access to genetic testing should not prevent clinically sound care. Conversely, routine inherited-thrombophilia, immune and infection panels are poor uses of scarce resources when their results are unlikely to alter management.

The treatment evidence points in the same direction. Aspirin and heparin have a clear role only in selected women, particularly those with APS, rather than as universal treatment for recurrent miscarriage. The ALIFE2 trial further weakens the rationale for heparin in inherited thrombophilia alone.¹⁶

Progesterone should also be matched to the clinical context: modern evidence supports vaginal micronised progesterone most clearly when previous miscarriage is accompanied by bleeding in the current early pregnancy.^{19,20} Routine progestogen prophylaxis for

unexplained RPL has not shown a convincing live-birth advantage in the updated Cochrane review.²¹

The role of dydrogesterone deserves further study in settings where oral therapy is more available than vaginal micronised progesterone. The current evidence is sufficient to justify discussion of its use in selected circumstances, but not to claim equivalence with the best-supported vaginal regimen. Routine prednisolone is even harder to justify because current guidelines do not support empirical immune treatment.^{1,2,22,23}

An evidence-based resource-adapted approach avoids two common errors: doing too little and missing a treatable disorder, or doing too much and exposing patients to costly investigations and medications of uncertain benefit. Future Nigerian and other African studies should evaluate the diagnostic yield and cost of simplified RPL pathways, access to APS testing, the feasibility of regional products-of-conception testing and pregnancy outcomes after structured early-pregnancy follow-up.

CONCLUSION

Recurrent first-trimester miscarriage in a resource-limited setting should be investigated selectively rather than superficially or exhaustively. A careful history, uterine ultrasound, thyroid-function testing, risk-directed metabolic assessment and appropriately prioritised APS testing provide a reasonable core. Genetic testing adds value when accessible, while routine inherited-thrombophilia, broad immune and infection panels should not consume the limited first-line investigation budget. Treatment should be equally selective. Folic acid remains standard preconception care. Aspirin and heparin should mainly be reserved for women with appropriately diagnosed APS. Vaginal micronised progesterone is best supported when bleeding occurs in a subsequent early intrauterine pregnancy in a woman with previous miscarriage. Dydrogesterone may be considered when the preferred regimen is unavailable or unsuitable, but the evidence is less secure, and routine prednisolone is not supported. The practical objective is not to reproduce every investigation or treatment available in a highly resourced centre. It is to identify the few interventions most likely to change outcome, provide early supportive follow-up and avoid exposing women to tests or medicines that add cost without clear benefit.

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