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# Diagnosis and management of idiopathic recurrent pregnancy loss (RPL): Current immune testing and immunomodulatory treatment practice in the United Kingdom

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ABSTRACT

Recurrent pregnancy loss (RPL) affects 1.9 % of couples. Despite the severe physical, psychological, and economic impact of RPL, miscarriage care provision remains highly heterogeneous. Due to the absence of strong scientific evidence, national and international guidelines on the diagnosis and treatment of this condition remain unclear and often contradictory. In the absence of identifiable RPL-associated risk factors, when the condition is termed "idiopathic", immunological tests and immunomodulatory treatments are sometimes suggested even though the contribution of aberrant immune activity to this condition remains undetermined. Through an online survey, distributed across the UK (37.7% response rate), a high variation in clinical practice was detected, with multiple RPL definitions utilized and different tests employed for potential risk factor identification. Immunological testing was found to be provided in 7.9 %($N = 3$) of the included clinics. Moreover, multiple therapies, including immunomodulatory ones were utilized for the management of idiopathic RPL. These findings highlight a need for additional research on the implication of immune activity in this condition. The high variation between clinics regarding the tests employed for the diagnosis and management of idiopathic RPL also underlines the need for guidelines to direct clinical practice, taking into consideration both the patients' needs but also the strength of the available scientific evidence.

## 1. Introduction

Recurrent pregnancy loss (RPL) affects 0.7%– 1.9% of women, causing significant psychological harm for couples and increasing the risk of adverse obstetric conditions (Quenby et al., 2021; Farren et al., 2018; Tavoli et al., 2018). The direct national economic impact of miscarriage approximates £ 471 million/year (Quenby et al., 2021).

There is marked heterogeneity in diagnostic guidelines, with the National Institute for Health and Care Excellence (NICE), Royal College of Obstetricians and Gynaecologists (RCOG), and German (DGGG), Austrian (ÖGGG), and Swiss (SGGG) Society of Gynecology and Obstetrics defining RPL as at least three consecutive pregnancy losses and the European Society of Human Reproduction and Embryology (ESHRE) diagnosing this condition upon two, not necessarily consecutive, losses (RCOG, 2011; NICE, 2020a; Toth et al., 2018; ESHRE et al., 2018). This variation makes interpreting existing scientific evidence more difficult.

RPL is multifactorial, with advanced maternal age and number of past losses considered primary risk factors (Quenby et al., 2021; ESHRE, 2017; RCOG, 2011; NICE, 2020c). Although additional risk factors, including chromosomal abnormalities and maternal pathologies, have been described (NICE, 2020c; ESHRE, 2017; RCOG, 2011), a causal relationship has not been established (Ewington et al., 2019; ESHRE, 2017). In ~50% of cases, termed "idiopathic", no risk factor is identified (NICE, 2020c; ASRM, 2012). The uncertainty regarding RPL pathogenesis has resulted in guidance and care variation, with multiple investigations and treatments being offered, despite the lack of sufficient supporting evidence (Coomarasamy et al., 2021; Manning et al., 2021).

Revised concepts regarding idiopathic RPL are emerging, with

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immune dysregulation at the forefront of much research activity (Guo et al., 2021; Wang et al., 2021). Peripheral and uterine Natural Killer (NK) cells have gained most interest, with elevated numbers and cytotoxic potential reported (Shakhar et al., 2003; Yoo et al., 2012). These cells are considered essential to pregnancy establishment, contributing to uterine remodeling and controlling trophoblast invasion (Ticconi et al., 2019; Moffett-King, 2002). However, the most recent ESHRE consensus highlights the lack of sufficient evidence supporting routine NK cell testing (ESHRE et al., 2018) as evidence remains heterogeneous (Wang et al., 2008; Michimata et al., 2002). A shift towards pro-inflammatory cytokine secretion by T helper cells has also been described in RPL (Carp, 2004; Raghupathy et al., 1999), although opposing findings have again been reported (Shimada et al., 2004; Reinhard et al., 1998). Additional observations regarding immune dysregulation in RPL include $CD4^+/CD8^+$ T cell ratio elevation (Marron et al., 2019), regulatory T cell (Treg) reduction (Wang et al., 2010), $CD5^+$ B cell increase (Muzzio et al., 2013), and anti-HLA and anti-HY antibody presence (Nielsen et al., 2010). Although understanding of immune dysregulation in RPL is evolving, current guidelines are consistent in their recommendations to restrict immune tests within the research setting (ESHRE et al., 2018; RCOG, 2011; The Miscarriage Association, 2020).

Given the burden of idiopathic RPL, both couples and clinicians are keen to identify new tests. The National Healthcare System (NHS) offers free tests and counselling, with clinics expected to follow specific guidelines, such as those provided by RCOG or NICE. Additional tests or treatments may sometimes be offered as part of research studies. Couples may choose to attend private practices offering a wider variety of diagnostic and therapeutic options, often at an increased cost. In the absence of a clear explanation for their loss, couples may be willing to seek treatment options for which the evidence is less robust.

The objective of this study was to understand current practice nationally with regards to the investigation and management of idiopathic RPL, focusing upon immune tests and immunomodulatory therapies.

## 2. Methods

### 2.1. Population

The survey was sent to RPL specialists in NHS and private miscarriage clinics across the UK. NHS-associated recipients were identified through the Tommy's Network, while private clinics were contacted following self-guided online research. Ethical approval was not required for this service evaluation.

### 2.2. Development and distribution

The survey (SmartSurvey™ ©2020) comprised 22 questions. Most questions were in closed-end multiple-choice format, with open-ended sections for additional information. To evaluate the efficiency/likelihood of offering certain treatments a five-point Likert scale matrix was utilized. The survey was piloted in the Tommy's National Centre for Miscarriage, University of Birmingham prior to a 3-stage dissemination process. In phase 1 the questionnaire was circulated electronically to 94 NHS-associated recipients, representing 60 clinics, and 14 private clinics (June 2020). In phase 2 the questionnaire was re-circulated to past and 40 additional NHS-associated recipients (July 2020). In phase 3 it was re-circulated to non-respondents (April 2022) (total clinics $N = 114$, total recipients $N = 148$).

### 2.3. Data analysis

Data were semi-anonymized with center information collected. Incomplete responses were considered when appropriate. The institution name and Internet Protocol address were used to identify duplicate responses. Results were presented in the form of descriptive statistics via Microsoft Excel (2016). The individual questions' response rates and each answer's percentage were calculated based on total responses obtained for each question. For Likert scale data, sub-question-specific response rates were determined and percentages were calculated accordingly. To compare treatment effectiveness, the Friedman test was utilized, alongside the Dunn's test for multiple comparisons.

## 3. Results

### 3.1. Demographics and official guidelines

Overall, 43 survey responses were collected (37.7 % clinic response rate, 29.1 % individual response rate) (Fig. 1, Supplementary Fig. 1). The respondent group comprised 72.2 %($N = 26$) Obstetrics and Gynaecology Consultants, 16.7 %($N = 6$) Nurses, 5.6 %($N = 2$) Associate Specialists, 2.8 %($N = 1$) Professor in Obstetrics and Gynaecology, and 2.8 %($N = 1$) Clinical Manager [Response rate= 83.7 %($N = 36$)]. 97.6 %($N = 41$) of clinics were NHS-associated and 2.4 %($N = 1$) belonged to the private sector [Response rate= 97.7 %($N = 42$)].

In total, 72.1 %($N = 31$) of clinics followed a specific protocol for RPL diagnosis and management [Response rate= 100 %($N = 43$)]. Of these clinics, 35.5 %($N = 11$) followed RCOG, 12.9 %($N = 4$) ESHRE, 3.2 %($N = 1$) NICE, and 19.4 %($N = 6$) followed local guidance. 3.2 %($N = 1$) of clinics used RCOG and ESHRE guidance and 3.2 %($N = 1$) utilized a combination of local and ESHRE guidelines.

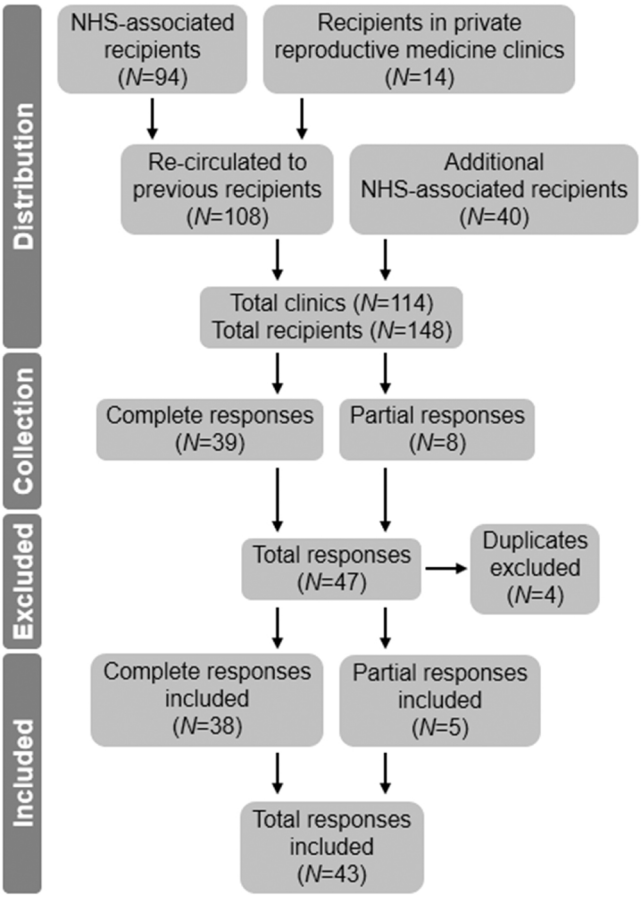


**Fig. 1.** Flow diagram detailing survey distribution and data collection. The strategy used for questionnaire distribution and response collection is displayed, alongside the number (N) of recipients and respondents. Duplicate responses were excluded.

### 3.2. RPL diagnostic criteria

With regards to eligibility criteria, most clinics would review women following 3 losses; 51.4 %($N = 19$), while 17(45.9%) accepted referrals following 2 (Fig. 2A). Eight respondents offered review to older women after 2 losses. In 53.5 %($N = 23$) of clinics, consecutive losses were a pre-requisite (Fig. 2B). Although most clinics reviewed women who had experienced biochemical loss (92.9 %,$N = 39$), $N = 3$(7.1 %) would not (Fig. 2C). Prior to referral, additional investigations, including thrombophilia screening ($N = 1$), antiphospholipid testing ($N = 1$), and 3D scanning ($N = 1$), were required in different clinics. In the private clinic ($N = 1$), any woman could self-refer without pre-specified criteria.

### 3.3. RPL investigations

Information on tests performed was provided by 38 clinics (Table 1). In all clinics, foetal karyotyping, anti-cardiolipin antibodies, and lupus anticoagulant testing were performed either routinely [foetal karyotyping: 73.7 %($N = 28$), anti-cardiolipin antibodies: 92.1 %($N = 35$), lupus anticoagulant: 92.1 %($N = 35$)] or when clinically indicated [foetal karyotyping: 26.3%($N = 10$), anti-cardiolipin antibodies: 7.9 %($N = 3$), lupus anticoagulant: 7.9 %($N = 3$)]. Pelvic ultrasonography [Routinely: 78.9 %($N = 30$), When indicated: 18.4 %($N = 7$)], thyroid-stimulating hormone (TSH) level assessment [Routinely: 78.9 %($N = 30$), When indicated: 15.8 %($N = 6$)] and parental karyotyping [Routinely: 15.8%($N = 6$), When indicated: 71.1 %($N = 27$)] were also commonly utilised (Table 1). Other tests, such as hysteroscopy (78.9 %, $N = 30$), hysterosalpingography (63.2 %,$N = 24$), anti-Müllerian hormone (39.5 %,$N = 15$), inhibin B (31.6 %,$N = 12$), and sperm DNA fragmentation (15.8 %,$N = 6$) were only performed when clinically indicated (Table 1). In addition, 13.2 %($N = 5$) reported using 3D ultrasonography and 5.3 %($N = 2$) using MRI for anatomical risk factor detection.

### 3.4. Immunological RPL investigations

Immunological testing was not routinely offered by any clinic. 3(7.9 %) clinics recommended NK cell cytotoxicity, NK, T, and B cell and $CD4^+/CD8^+$ T cell immunophenotyping, and T helper cell cytokine production evaluation when indicated (Table 2). The conditions guiding such recommendation were not specified. These respondents represented two NHS-affiliated and one private clinic, located in different regions. The two NHS clinics also performed Treg and $CD5^+/CD5^-$ B cell immunophenotyping, HLA-typing, and anti-HY, anti-HLA, and paternal blocking antibody screening (Table 2). Anti-nuclear antibody screening was offered routinely in 6(15.8 %) clinics and when indicated in 8 (21.1%), while anti-smooth muscle (21.1 %,$N = 8$) and anti-sperm (13.2 %,$N = 5$) antibody testing was only performed when clinically indicated (Table 2). Endometrial testing was offered in 3(3.1 %) NHS-associated clinics, as part of a trial ($N = 1$) or a private service ($N = 1$).

### 3.5. Idiopathic RPL management

Information on idiopathic RPL management was received from 32 clinics (Table 3). Supportive care and lifestyle changes were the most widely practiced (89.5 %,$N = 34$). Treatments including folic acid (76.3 %,$N = 29$), progesterone (71.1 %,$N = 27$), aspirin (63.2 %,$N = 24$), vitamin D (57.9 %,$N = 22$), and heparin (47.4 %,$N = 18$) were also commonly utilised (Table 3).

Third-party donor and paternal cell immunization or trophoblast membrane infusion were not offered by any clinic. In the private clinic, intralipid infusion, anti-tumor necrosis factor (TNF)-α agents, granulocyte-colony stimulating factor (G-CSF), and tacrolimus used to be offered, although exact indications for their use were not reported.

Assessment of current perspectives regarding the efficacy of potential treatments, revealed most are considered ineffective and are unlikely to be recommended (Table 4). Folic acid and progesterone were considered significantly more effective than most treatments included and more likely to be suggested for idiopathic RPL management (Supplementary Fig. 2, $p < 0.05$).

A discordance between treatment ratings and clinical practice was however identified. For instance, aspirin ($N = 2$), prednisone ($N = 1$), prednisolone ($N = 1$), vitamin D ($N = 1$), and multivitamins ($N = 1$) were each described as not effective by clinics utilising such treatments. Conversely, progesterone ($N = 2$), intralipid ($N = 1$), vitamin D ($N = 2$), and multivitamin supplementation ($N = 5$) were described as very/often effective by clinics not offering such treatments.

## 4. Discussion

We demonstrate marked variations in current RPL investigation and management across the UK. Consistent with recent reports calling for an international consensus regarding miscarriage care (Manning et al., 2021; Coomarasamy et al., 2021), present data clearly reflects significant heterogeneity in service provision. Uniquely, this questionnaire focused upon idiopathic RPL, examining the use of immunological testing and immunomodulatory treatments. Accessibility to specialist services was highly disparate with marked differences in both the RPL definition and referral criteria adopted. This variance most likely reflects the stark lack of consensus between current guidelines and our data clearly demonstrate marked differences in guideline uptake. ESHRE guidance recommends investigation of women with 2 losses (ESHRE et al., 2018). However, this was only reported at 7 sites. Conversely, RCOG and NICE advise that women should be referred after experiencing 3 consecutive miscarriages (RCOG, 2011; NICE, 2020a). This variation is similarly observed internationally, with the American

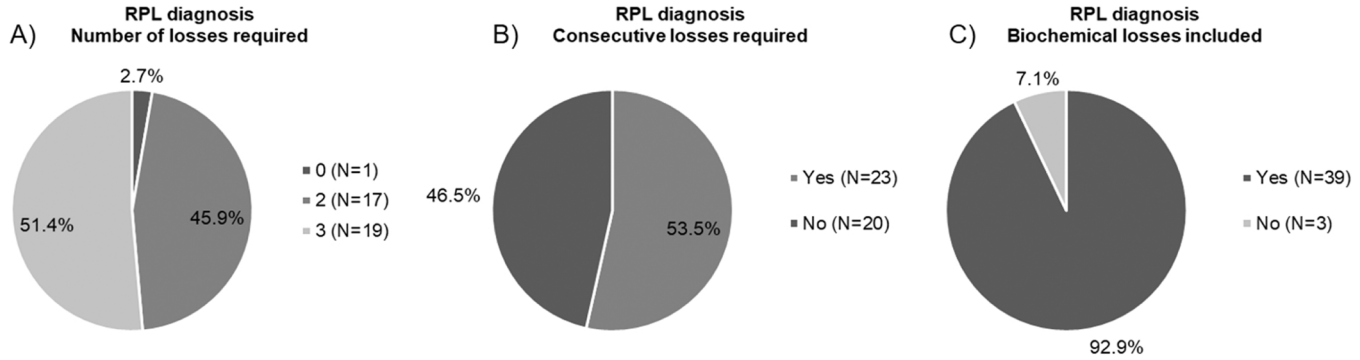


**Fig. 2.** Diagnostic criteria for the review of women in recurrent pregnancy loss clinics. Total response number (N) and percentage (%) calculated according to total responses for each question are shown [Number of losses required response rate= 86%(N = 37), Consecutive losses required response rate= 100%(N = 43), Biochemical losses included response rate= 97.7%(N = 42)].

**Table 1**
Summary of diagnostic tests performed for the investigation of recurrent pregnancy loss (RPL). Routine and clinically indicated investigations performed are summarised, with the response number (N) and percentage (%), calculated based on the total number of responses obtained for the respective question, shown [Response rate= 88.4%(N = 38)].

| Tests performed for the investigation of RPL-associated risk factors | *N* (%) | |
|---|---|---|
| | Routinely | When clinically indicated |
| Anatomical | | |
| Pelvic ultrasonography | 30 (78.9 %) | 7 (18.4 %) |
| Hysteroscopy | 0 (0 %) | 30 (78.9 %) |
| Hysterosalpingography (HSG) | 0 (0 %) | 24 (63.2 %) |
| Genetic/chromosomal | | |
| Maternal karyotyping | 6 (15.8 %) | 27 (71.1 %) |
| Paternal karyotyping | 6 (15.8 %) | 27 (71.1 %) |
| Foetal karyotyping | 28 (73.7 %) | 10 (26.3 %) |
| Haematological | | |
| Anti-β glycoprotein antibodies | 16 (42.1 %) | 6 (15.8 %) |
| Anti-cardiolipin antibodies | 35 (92.1 %) | 3 (7.9 %) |
| Lupus anticoagulant | 35 (92.1 %) | 3 (7.9 %) |
| Antiphosphatidic acid | 2 (5.3 %) | 8 (21.1 %) |
| Antiphosphatidyl serine | 1 (2.6 %) | 8 (21.1 %) |
| Antiphosphatidyl ethanolamine | 1 (2.6 %) | 7 (18. 4 %) |
| Antiphosphatidyl choline | 1 (2.6 %) | 7 (18. 4 %) |
| Antiphosphatidyl glycerol | 1 (2.6 %) | 7 (18. 4 %) |
| Antiphosphatidyl inositol | 1 (2.6 %) | 7 (18. 4 %) |
| Prothrombin Time (PT) | 20 (52.6 %) | 6 (15. 8 %) |
| Activated Partial Thromboplastin Time (aPTT) | 20 (52.6 %) | 6 (15. 8 %) |
| Activated protein C resistance | 13 (34.2 %) | 10 (26.3 %) |
| Protein C deficiency | 18 (47.4 %) | 11 (28.9 %) |
| Protein S deficiency | 18 (47.4 %) | 12 (31.6 %) |
| Factor V Leiden | 19 (50 %) | 11 (28.9 %) |
| Antithrombin (III) deficiency | 16 (42.1 %) | 10 (26.3 %) |
| tMTHFR Gene Mutation | 4 (10.5 %) | 10 (26.3 %) |
| Prothrombin gene mutation | 13 (34.2 %) | 10 (26.3 %) |
| Hypothalamic-pituitary-ovarian axis | | |
| Progesterone | 4 (10.5 %) | 17 (44.7 %) |
| Luteinizing hormone (LH) | 6 (15.8 %) | 19 (50 %) |
| Prolactin | 5 (13.2 %) | 18 (47.4 %) |
| Follicle-stimulating hormone (FSH) | 6 (15.8 %) | 19 (50 %) |
| Anti-Müllerian hormone (AMH) | 0 (0 %) | 15 (39.5 %) |
| Oestrogen | 5 (13.2 %) | 16 (42.1 %) |
| Testosterone | 4 (10.5 %) | 17 (44.7 %) |
| Free androgen index | 4 (10.5 %) | 18 (47.4 %) |
| Sex hormone binding globulin (SHBG) | 3 (7.9 %) | 20 (52.6 %) |
| Inhibin B | 0 (0 %) | 12 (31.6 %) |
| Thyroid-associated | | |
| Anti-thyroid peroxidase (anti-TPO) antibodies | 11 (28.9 %) | 13 (34.2 %) |
| Anti-thyroglobulin (anti-Tg) antibodies | 1 (2.6 %) | 12 (31.6 %) |
| Triiodothyronine (T3) | 13 (34.2 %) | 12 (31.6 %) |
| Thyroxine (T4) | 17 (44.7 %) | 11 (28.9 %) |
| Thyroid stimulating hormone (TSH) | 30 (78.9 %) | 6 (15.8 %) |
| Diabetes | | |
| Random venous glucose | 1 (2.6 %) | 17 (44.7 %) |
| Glycated haemoglobin (HbA1c) | 12 (31.6 %) | 12 (31.6 %) |
| Infection | | |
| Low vaginal microbiology swab | 1 (2.6 %) | 20 (52.6 %) |
| High vaginal swab (endocervical) | 3 (7.9 %) | 16 (42.1 %) |
| High vaginal swab (ectocervical) | 3 (7.9 %) | 17 (44.7 %) |
| Other | | |
| Sperm DNA fragmentation | 0 (0 %) | 6 (15.8 %) |
| Vitamin D (25OHD3) levels | 4 (10.5 %) | 8 (21.1 %) |
| Homocysteine levels | 2 (5.3 %) | 6 (15.8 %) |

**Table 2**
Summary of diagnostic tests performed for the investigation of immunological factors associated with recurrent pregnancy loss (RPL). Routine and clinically indicated investigations performed are shown, with the number of responses (N) and percentage (%), calculated according to the total number of responses for the respective question, depicted [Response rate= 88.4%(N = 38)].

| Tests performed for the investigation of immunological RPL-associated risk factors | Routinely *N* (%) | When clinically indicated *N* (%) |
|---|---|---|
| Assessment of Natural Killer (NK) cell cytotoxicity | 0 (0 %) | 3 (7.9 %) |
| NK, T, and B cell immunophenotyping | 0 (0 %) | 3 (7.9 %) |
| $CD4^+$ helper ($T_H$) and $CD8^+$ cytotoxic ($T_C$) T cell immunophenotyping | 0 (0 %) | 3 (7.9 %) |
| Regulatory T cell (Treg) immunophenotyping | 0 (0 %) | 2 (5.3 %) |
| Examination of $T_H$ cell cytokine production | 0 (0 %) | 3 (7.9 %) |
| $CD5^+$ (B-1) and $CD5^-$ (B-2) B cell immunophenotyping | 0 (0 %) | 2 (5.3 %) |
| Anti-HY antibody screening | 0 (0 %) | 2 (5.3 %) |
| Anti-Human Leukocyte antigen (HLA) antibody screening | 0 (0 %) | 2 (5.3 %) |
| Anti-paternal blocking antibody screening | 0 (0 %) | 2 (5.3 %) |
| HLA-typing (DQα sharing) | 0 (0 %) | 2 (5.3 %) |
| Anti-nuclear antibodies (ANA) (e.g. anti-DNA, anti-histone, anti-Sm, anti-ribonucleoprotein, anti-Jo, anti-Scl, anti-SSA/Ro, anti-SSB/La) | 6 (15.8 %) | 8 (21.1 %) |
| Anti-smooth muscle antibodies | 0 (0 %) | 8 (21.1 %) |
| Anti-sperm antibodies (maternal) | 0 (0 %) | 5 (13.2 %) |
| Anti-sperm antibodies (paternal) | 0 (0 %) | 5 (13.2 %) |

College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine (ASRM) suggesting assessment of women with at least 2 clinical losses and the DGGG, ÖGGG, SGGG, French, Northern Ireland Public Health Agency, Queensland, and Ministry of Health & Family Welfare Government of India defining RPL as 3 or more losses (ACOG, 2018; ASRM, 2012; Toth et al., 2018; Huchon et al., 2016; Benson et al., 2021; Queensland Clinical Guidelines, 2018; Ministry of Health and Family Welfare Government of India, 2017). With novel evidence highlighting an exponential increase in miscarriage risk, earlier investigation and intervention may be recommended (Coomarasamy et al., 2021; van Dijk et al., 2020).

Considering RPL investigations, marked variation was identified. Tests including antiphospholipid antibody screening, pelvic ultrasonography, TSH measurement, and foetal karyotyping are routinely offered in 73.7 %– 92.1 % of clinics, consistent with official guidance (ESHRE, 2017; RCOG, 2011; NICE, 2020b). Although not investigated in the present study, foetal karyotyping is most often performed for the pregnancy upon or following patient attendance at an early pregnancy assessment unit. Abnormal findings are commonly followed by parental karyotyping (Manning et al., 2021). However, retrospective investigation of stored products of conception cannot be excluded. Hypothalamic-pituitary-ovarian axis, infection, and diabetes assessments were routinely offered in some clinics, in contrast to recommendations (ESHRE, 2017). Specialist centres were more likely to offer these investigations "when clinically indicated". Greater disparity was seen with regards to haematological testing, with some centres routinely offering comprehensive thrombophilia screening. Antiphospholipid

**Table 3**
Treatments offered for idiopathic recurrent pregnancy loss (RPL) management. The total response number (N) and percentage (%) calculated according to the total responses is included [Response rate= 88.4 %(N = 38)].

| Idiopathic RPL management | *N* (%) |
|---|---|
| Aspirin | 24 (63.2 %) |
| Prednisone | 1 (2.6 %) |
| Prednisolone | 5 (13.2 %) |
| Progesterone | 27 (71.1 %) |
| Human chorionic gonadotropin (hCG) | 1 (2.6 %) |
| Anti-Tumour Necrosis Factor (TNF)-α agents | 1 (2.6 %) |
| Granulocyte-colony stimulating factor (G-CSF) | 1 (2.6 %) |
| Hydroxychloroquine | 5 (13.2 %) |
| Heparin | 18 (47.4 %) |
| Intravenous immunoglobulin (IVIg) | 2 (5.3 %) |
| Paternal cell immunization | 0 (0 %) |
| Third-party donor leukocyte immunization | 0 (0 %) |
| Trophoblast membrane infusion | 0 (0 %) |
| Intralipid infusion | 1 (2.6 %) |
| Endometrial scratching | 3 (7.9 %) |
| Folic acid | 29 (76.3 %) |
| Vitamin D supplementation | 22 (57.9 %) |
| Multivitamin supplementation | 10 (26.3 %) |
| Psychotherapy | 9 (23.7 %) |
| Supportive care | 34 (89.5 %) |
| Lifestyle changes (e.g. in case of obesity, high alcohol intake, illicit drug use, smoking) | 34 (89.5 %) |

syndrome is a recognised cause of RPL, with consistent recommendations regarding investigation using anti-cardiolipin and lupus anticoagulant with or without β2 glycoprotein I. Although data regarding other antiphospholipid assays, including phosphatidic acid and phosphatidyl choline, ethanolamine, glycerol, inositol, and serine is quite limited, a notably high number of centres measure these antibodies "when clinically indicated". Inherited thrombophilia screening was highly heterogenic, with many centres offering detailed screens. This likely reflect differences in current ESHRE and RCOG guidance (ESHRE et al., 2018; RCOG, 2011), with ALIFE2 trial data much anticipated (https://warwick.ac.uk/fac/sci/med/research/ctu/trials/alife2/).

Importantly, consistent with current guidance, immunological testing is not routinely performed in the UK (ESHRE et al., 2018; RCOG, 2011). For women with idiopathic RPL, immunological testing was only offered at 3 clinics. We anticipate this reflects a paucity of high-quality evidence, with more robust phenotypic and functional analyses of immune cell subsets in RPL warranted to support routine assessment.

With regards to idiopathic RPL management, lifestyle changes and supportive care emerged as the most used tools. Progesterone and folic acid were rated as most effective, being more likely to be offered. Progesterone use for idiopathic RPL management was suggested in two systematic reviews and meta-analyses (Roepke et al., 2018; Saccone et al., 2017). A high percentage of respondents identified vitamin D and multivitamin supplementation as effective treatments they would definitely suggest, which may reflect routine antenatal care guidance (NICE, 2021). Interestingly, only ~60% confirmed vitamin D use. Whether this reflects low-dose supplementation or higher treatment doses is unclear but of interest. Aspirin appears widely utilised for idiopathic RPL management. Some evidence suggest that aspirin may increase the risk of miscarriage in women without thrombophilia and empirical treatment is not supported (ESHRE et al., 2018; de Jong et al., 2014; Coomarasamy et al., 2021). The private clinic representative highlighted that according to latest regulations, private practices are not allowed to prescribe immune treatments, such as anti-TNF-α agents and G-CSF which were previously recommended. Although further information

**Table 4**
Estimated efficiency and likelihood to suggest different treatments for idiopathic recurrent pregnancy loss management. The total response number (N) and percentage (%) calculated according to the total responses for each treatment is illustrated. Each treatment's response rate is also shown.

| Treatment | Treatment efficiency/ Likelihood to suggest | *N* (%) | Response rate *N* (%) |
|---|---|---|---|
| Aspirin | Not effective/Would not suggest | 13 (39.4 %) | 33 (76.7 %) |
| | Rarely effective/Would probably not suggest | 1 (3 %) | |
| | Somewhat effective/ Could suggest depending on the case | 8 (24.2 %) | |
| | Often effective/Would probably suggest | 5 (15.2 %) | |
| | Very effective/Would definitely suggest | 6 (18.2 %) | |
| Other non-steroidal anti-inflammatory drugs | Not effective/Would not suggest | 26 (92.9 %) | 28 (65.1 %) |
| | Rarely effective/Would probably not suggest | 1 (3.6 %) | |
| | Somewhat effective/ Could suggest depending on the case | 1 (3.6 %) | |
| | Often effective/Would probably suggest | 0 (0 %) | |
| | Very effective/Would definitely suggest | 0 (0 %) | |
| Prednisone | Not effective/Would not suggest | 23 (82.1 %) | 28 (65.1 %) |
| | Rarely effective/Would probably not suggest | 3 (10.7 %) | |
| | Somewhat effective/ Could suggest depending on the case | 2 (7.1 %) | |
| | Often effective / Would probably suggest | 0 (0 %) | |
| | Very effective/Would definitely suggest | 0 (0 %) | |
| Prednisolone | Not effective/Would not suggest | 18 (66.7 %) | 27 (62.8 %) |
| | Rarely effective/Would probably not suggest | 5 (18.5 %) | |
| | Somewhat effective/ Could suggest depending on the case | 3 (11.1 %) | |
| | Often effective/Would probably suggest | 0 (0 %) | |
| | Very effective/Would definitely suggest | 1 (3.7 %) | |
| Other steroids | Not effective/Would not suggest | 22 (88 %) | 25 (58.1 %) |
| | Rarely effective/Would probably not suggest | 1 (4 %) | |
| | Somewhat effective/ Could suggest depending on the case | 1 (4 %) | |
| | Often effective/Would probably suggest | 1 (4 %) | |
| | Very effective/Would definitely suggest | 0 (0 %) | |
| Progesterone | Not effective/Would not suggest | 5 (13.9 %) | 36 (83.7 %) |
| | Rarely effective/Would probably not suggest | 2 (5.6 %) | |
| | Somewhat effective/ Could suggest depending on the case | 14 (38.9 %) | |
| | Often effective/Would probably suggest | 11 (30.6 %) | |

(*continued on next page*)

**Table 4** (*continued*)

| Treatment | Treatment efficiency/ Likelihood to suggest | *N* (%) | Response rate *N* (%) |
|---|---|---|---|
| | Very effective/Would definitely suggest | 4 (11.1 %) | |
| Human Chorionic Gonadotropin (hCG) | Not effective/Would not suggest | 22 (84.6 %) | 26 (60.5 %) |
| | Rarely effective/Would probably not suggest | 3 (11.5 %) | |
| | Somewhat effective / Could suggest depending on the case | 1 (3.8 %) | |
| | Often effective/Would probably suggest | 0 (0 %) | |
| | Very effective/Would definitely suggest | 0 (0 %) | |
| Other Hormonal treatment | Not effective/Would not suggest | 22 (91.7 %) | 24 (55.8 %) |
| | Rarely effective/Would probably not suggest | 2 (8.3 %) | |
| | Somewhat effective/ Could suggest depending on the case | 0 (0 %) | |
| | Often effective/Would probably suggest | 0 (0 %) | |
| | Very effective/Would definitely suggest | 0 (0 %) | |
| Anti-Tumour Necrosis Factor (TNF)-α agents | Not effective/Would not suggest | 25 (100 %) | 25 (58.1 %) |
| | Rarely effective/Would probably not suggest | 0 (0 %) | |
| | Somewhat effective/ Could suggest depending on the case | 0 (0 %) | |
| | Often effective/Would probably suggest | 0 (0 %) | |
| | Very effective/Would definitely suggest | 0 (0 %) | |
| Granulocyte-Colony Stimulating factor (G-CSF) | Not effective/Would not suggest | 23 (92 %) | 25 (58.1 %) |
| | Rarely effective/Would probably not suggest | 1 (4 %) | |
| | Somewhat effective/ Could suggest depending on the case | 0 (0 %) | |
| | Often effective/Would probably suggest | 1 (4 %) | |
| | Very effective/Would definitely suggest | 0 (0 %) | |
| Paternal cell immunization | Not effective/Would not suggest | 24 (100 %) | 24 (55.8 %) |
| | Rarely effective/Would probably not suggest | 0 (0 %) | |
| | Somewhat effective/ Could suggest depending on the case | 0 (0 %) | |
| | Often effective/Would probably suggest | 0 (0 %) | |
| | Very effective/Would definitely suggest | 0 (0 %) | |
| Third-party donor leukocyte immunization | Not effective/Would not suggest | 24 (100 %) | 24 (55.8 %) |
| | Rarely effective/Would probably not suggest | 0 (0 %) | |
| | Somewhat effective/ Could suggest depending on the case | 0 (0 %) | |
| | Often effective/Would probably suggest | 0 (0 %) | |
| | Very effective/Would definitely suggest | 0 (0 %) | |
| Vitamin D supplementation | Not effective/Would not suggest | 7 (24.1 %) | 29 (67.4 %) |
| | Rarely effective/Would probably not suggest | 0 (0 %) | |
| | Somewhat effective/ Could suggest depending on the case | 4 (13.8 %) | |
| | Often effective/Would probably suggest | 6 (20.7 %) | |
| | Very effective/Would definitely suggest | 12 (41.4 %) | |
| Multivitamin supplementation | Not effective/Would not suggest | 10 (40 %) | 25 (58.1 %) |
| | Rarely effective/Would probably not suggest | 0 (0 %) | |
| | Somewhat effective/ Could suggest depending on the case | 3 (12 %) | |
| | Often effective/Would probably suggest | 2 (8 %) | |
| | Very effective/Would definitely suggest | 10 (40 %) | |
| Folic acid | Not effective/Would not suggest | 5 (16.1 %) | 31 (72.1 %) |
| | Rarely effective/Would probably not suggest | 0 (0 %) | |
| | Somewhat effective/ Could suggest depending on the case | 3 (9.7 %) | |
| | Often effective/Would probably suggest | 4 (12.9 %) | |
| | Very effective/Would definitely suggest | 19 (61.3 %) | |
| Hydroxychloroquine | Not effective/Would not suggest | 19 (82.6 %) | 23 (53.5 %) |
| | Rarely effective/Would probably not suggest | 1 (4.3 %) | |
| | Somewhat effective/ Could suggest depending on the case | 2 (8.7 %) | |
| | Often effective/Would probably suggest | 0 (0 %) | |
| | Very effective/Would definitely suggest | 1 (4.3 %) | |
| Heparin | Not effective/Would not suggest | 12 (38.7 %) | 31 (72.1%) |
| | Rarely effective/Would probably not suggest | 1 (3.2 %) | |
| | Somewhat effective/ Could suggest depending on the case | 9 (29 %) | |
| | Often effective/Would probably suggest | 3 (9.7 %) | |
| | Very effective/Would definitely suggest | 6 (19.4 %) | |
| Intravenous Immunoglobulin (IVIg) | Not effective/Would not suggest | 22 (91.7 %) | 24 (55.8 %) |
| | Rarely effective/Would probably not suggest | 1 (4.2 %) | |
| | Somewhat effective/ Could suggest depending on the case | 0 (0 %) | |
| | Often effective/Would probably suggest | 1 (4.2 %) | |
| | Very effective/Would definitely suggest | 0 (0 %) | |
| Trophoblast membrane infusion | Not effective/Would not suggest | 24 (100 %) | 24 (55.8 %) |
| | Rarely effective/Would probably not suggest | 0 (0 %) | |
| | Somewhat effective/ Could suggest depending on the case | 0 (0 %) | |

(*continued on next page*)

**Table 4** (*continued*)

| Treatment | Treatment efficiency/ Likelihood to suggest | *N* (%) | Response rate *N* (%) |
|---|---|---|---|
| | Often effective/Would probably suggest | | |
| | Very effective/Would definitely suggest | 0 (0 %) | |
| Intralipid infusion | Not effective/Would not suggest | 22 (88 %) | 25 (58.1 %) |
| | Rarely effective/Would probably not suggest | 1 (4 %) | |
| | Somewhat effective/ Could suggest depending on the case | 0 (0 %) | |
| | Often effective/Would probably suggest | 1 (4 %) | |
| | Very effective/Would definitely suggest | 1 (4 %) | |
| Endometrial scratching | Not effective/Would not suggest | 21 (87.5 %) | 24 (55.8 %) |
| | Rarely effective/Would probably not suggest | 2 (8.3 %) | |
| | Somewhat effective/ Could suggest depending on the case | 1 (4.2 %) | |
| | Often effective/Would probably suggest | 0 (0 %) | |
| | Very effective/Would definitely suggest | 0 (0 %) | |

was not provided, the latest consensus statement between the Human Fertilisation & Embryology Authority, ESHRE, RCOG, Association of Biomedical Andrologists, Association of Clinical Embryologists, British Andrology Society, British Fertility Society, British Infertility Counselling Association, Fertility Network UK, Royal College of Nursing, and Senior Infertility Nurse Group, concludes that immune therapies for fertility patients, including intravenous immunoglobulin (IVIg), TNF blockers, steroids, and intralipid, are associated with considerable risks and no increased live birth rates, restricting their use to the research setting (Sanders et al., 2019).

Most immunomodulatory treatments included were not widely used and considered ineffective, reflecting national and international guidance recommending their use remains limited to research (ESHRE et al., 2018; RCOG, 2011; ASRM, 2012; Toth et al., 2018). There was however some discordance between ratings and clinical practice, possibly as a result of the limited therapeutic options and the high cost of certain treatments. This is similarly reflected in latest draft RCOG guidance (https://www.rcog.org.uk/en/guidelines-research-services/guidelines/consultation-documents/). The lack of strong evidence reinforcing most potential immunomodulatory RPL treatments, including aspirin, IVIg, leukocyte immunization, and intralipid has been underlined (Coomarasamy et al., 2021; Carp, 2019; Roepke et al., 2018), with significant side-effects highlighted (Christiansen et al., 1994; Duhem et al., 1994). A recent systematic review and meta-analysis on subfertility and assisted reproduction concluded that randomized control trial (RCT) evidence available are inadequate to support immunomodulatory agent use, although emphasizing the possibility of a therapeutic benefit on certain patient subgroups (Melo et al., 2022).

Although beyond the scope of the present study, the economic impact of testing and treatment should be taken into consideration. In the private setting the cost of immunological testing can range from £ 160, for standard immunophenotyping, to approximately £ 450 for cytotoxicity and cytokine assessment, according to clinics' websites. Increased prevalence of such tests in private clinics is thus expected. Accordingly, increased cost appears to influence the therapeutic approach, with cheaper treatments, such as folic acid, vitamin supplementation, and aspirin being more likely to be suggested (Supplementary table 1), despite the lack of supporting literature. Cost may influence the therapeutic strategy, due to the lack of sufficient data from RCTs, although it is not expected to constitute a major factor directing clinical practice.

Additional RCTs are essential to demonstrate the efficacy and safety of immunomodulatory treatments for the management of idiopathic RPL, determine the optimal timing and dose, and more accurately define women most likely to benefit from such therapeutic approaches. Well-conducted qualitative research exploring couples' perspectives regarding idiopathic RPL investigation and management is important.

### 4.1. Limitations and future research

Present findings captured practice in NHS-associated clinics, with only one private clinic responding. Although the survey targeted a large recipient number, a relatively low response rate was achieved. Response collection was possibly affected by staff availability during the COVID-19 pandemic. No official private UK miscarriage clinic list was available and thus clinics were reached via their contact emails. Hence, private clinic response rate may have been affected by the communication strategy. Wider distribution, particularly to private clinics would allow a valuable insight into the range of diagnostic tests and immunotherapies offered, contributing to the efficacy and safety evaluation of different treatments.

A significant percentage of respondents reported the absence of an established protocol. The reason behind this phenomenon should be explored through further studies to determine whether clinical practice is influenced by the lack of a strong scientific rationale behind current recommendations or by the presence of multiple guidelines. Moreover, to reduce response time and thus increase the response rate, treatment efficiency/likelihood to suggest were combined into one question. However, such approach limits information obtained. Although semi-anonymised data were obtained and a mixture of closed- and open-ended questions were used, response bias should always be taken into consideration.

The exact treatment regimens used and additional treatment indications were not explored. Furthermore, clinical care regardless of miscarriage trimester was investigated, potentially contributing to the variation observed. Following surveys separately assessing first- and second-trimester losses could provide a more detailed insight into current practice.

Simultaneously, additional research is required to describe the potential implication of immune activity in RPL, potentially uncovering novel diagnostic and prognostic biomarkers. Current assays should also be standardized across laboratories.

The present survey was focused on clinical practice in the UK, where different guidelines are available. The high variability in test and treatments utilized locally indicates a possible international variation in miscarriage care. International questionnaire distribution would allow the assessment of differences in practice between countries, contributing to international guideline establishment.

## Conflict of interest

The authors of the paper certify that they have no affiliations with any organization or entity with financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jri.2022.103662.

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