would provide sufficient insight for clinical use. However, tests have emerged that focus on specific aspects of endometrial function. One such test entails the analysis of a panel of genes associated with endometrial receptivity from an endometrial biopsy taken during the putative WOI. Transcription of these genes is quantified and interpreted to report the endometrium as either pre-receptive, receptive, or post-receptive. Information relating to the response of the endometrium to progesterone exposure can be provided by histological assessment of Noyes' criteria, but this has been shown to be too subjective for clinical use. Since then, several other endometrial receptivity tests similarly focussing on measuring maturation have been marketed. Recently, a comprehensive in-depth analysis of all the transcriptomic panels investigated for their association with impaired endometrial receptivity has supported the hypothesis that RIF might be due to both displacement and disruption of the WOI (Koot *et al.*, 2016). This implies that a test aimed at assessing only one aspect will be of limited utility (Sebastian-Leon *et al.*, 2018).

A meta-analysis from 2022 included 11 studies and reported that the prevalence of displaced WOI, as detected through endometrial receptivity tests, was 34% (95% CI 24–43%) in RIF/poor prognosis patients (Liu *et al.*, 2022b). In patients with RIF, comparable ongoing pregnancy rates (OPR)/LBR were found between those with diagnosed non-receptive endometrium undergoing personalized ET (p-ET) and those with receptive endometrium undergoing routine ET (40.7% versus 49.6%; odds ratio (OR) 0.94; 95% CI 0.70–1.26; 6 studies; $n = 2552$) (Liu *et al.*, 2022b). In a more recent multicentre cohort study in patients with a single previous failed transfer, LBR and cumulative LBR were reported to be higher after unguided ET compared to p-ET, for both autologous and donor transfers (Cozzolino *et al.*, 2022).

A propensity score-matching approach adopted to limit the effect of putative confounders showed no significant improvement in clinical outcomes after using an endometrial receptivity test for p-ET (Bergin *et al.*, 2021). A recent 5-year multicentre RCT comparing p-ET after endometrial receptivity testing to fresh and frozen ET without the test showed comparable outcomes per transfer. Only in a per-protocol analysis, were higher cumulative LBRs in the p-ET reported (Simón *et al.*, 2020).

There is insufficient evidence to support the routine use of the currently available endometrial receptivity testing in ART and more studies are required to discern its value in identifying and enabling the treatment of endometrial maturation defects in women presenting with RIF. It is possible that, in the future, a more comprehensive assessment of endometrial receptivity through a combination of tests may be of benefit in the context of RIF (Hernández-Vargas *et al.*, 2020). Tests of endometrial receptivity increasingly assess other aspects. One example is a test for 'uterine immunological activation' based on RT–PCR analysis of a range of factors considered to be involved in differentiation of the secretory endometrium to the receptive state (Lédée *et al.*, 2017). While this test remains to be subject to assessment in RCTs, cohort studies (Lédée *et al.*, 2020) have suggested that it may have a role in the diagnostic workup of the endometrium in RIF, as indeed may other emerging tests. Moreover, increasing evidence is emerging for the role of decidualized endometrium acting as a gatekeeper to implantation after the epithelial layer is breached. Novel markers of this function are being developed (Muter *et al.*, 2021).

While there are insufficient data to recommend the routine use of any commercially available test of endometrial receptivity to diagnose the cause of RIF, assessment of specific aspects of endometrial function by testing can be considered.

Investigating chronic endometritis

Chronic endometritis (CE) has been described in patients with RIF with bacterial colonization, but also in women without clinical signs of infection and can lower the pregnancy rate (Johnston-MacAnanny *et al.*, 2010; Kitaya *et al.*, 2014, 2019; Cicinelli *et al.*, 2015; Bouet *et al.*, 2016; Kushnir *et al.*, 2016; Song *et al.*, 2018; Li *et al.*, 2020; Saxtorph *et al.*, 2020; Zargar *et al.*, 2020). It can be diagnosed by hysteroscopy, haematoxylin and eosin staining, and CD138-labelling (Kitaya *et al.*, 2014, 2019). Other diagnostic tests for endometritis include chromohysteroscopy (methylene blue dying of endometrium during hysteroscopy), bacterial culture, and molecular techniques such as PCR, RT–PCR, and next-generation sequencing (NGS) (Küçük and Safali, 2008; Moreno *et al.*, 2018). Nowadays, CE (and vaginal infection) seems to be routinely investigated in clinical practice (85% of clinicians) (Cimadomo *et al.*, 2021), even if there are limitations to histology in general, a lack of standardization of the concentration of plasma cells that should be regarded as a threshold (e.g. >1 or >5 plasma cells per high power field), and available studies often include only small numbers of patients or lack controls.

Antibiotics can be considered for the treatment of CE. Recent reviews on the topic, with different inclusion criteria and overlap in the studies included, reported conflicting results. Based on data from four studies, one systematic review reported significantly higher LBR/OPR (OR 5.33; 95% CI 2.41–11.79; $I^2 = 0\%$) in patients with cured CE (treated with antibiotics) compared to those with persistent CE (Vitagliano *et al.*, 2022). Another review calculated the LBR/OPR was not significantly higher in RIF patients with cured CE (after oral antibiotics) compared to those with persistent CE (OR 2.90; 95% CI 0.65–12.98; $I^2 = 77\%$; 4 studies) (Cheng *et al.*, 2022). The reviewers did report higher CPR in cured compared to persistent CE. A third review concluded oral antibiotic treatment for CE did not improve PR or LBR (Kato *et al.*, 2022).

At present, conclusions regarding the value of the diagnosis and treatment of endometritis are significantly hampered by the lack of standardization. However, the investigation and treatment of CE can be considered in RIF. Revision of this recommendation may be indicated should studies using more standardized diagnostic techniques, including the emerging DNA-based tests, reveal a clearer benefit.

Assessment for chronic endometritis (CE) can be considered. If CE is diagnosed, treatment with antibiotics can be considered.

Re-assessment of endometrial thickness

In clinical practice, 90% of clinicians considered the evaluation of endometrial thickness (EMT) relevant in RIF investigations (Cimadomo *et al.*, 2021). This reflects, in part, the ease of assessing this parameter.

A recent systematic review and meta-analysis investigating the association between endometrial thickness and LBR in fresh cycles reported that women with a thin endometrium (EMT < 7 mm) had a significantly lower LBR compared to women