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DEBATE—CONTINUED

Unexplained infertility: does it really exist? Does it matter?

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Unexplained infertility (UI) refers to a diagnosis made in couples in whom standard investigations including semen analysis, tests of ovulation and tubal patency are normal. It has been suggested that the term UI is unsustainable, as conditions such as endometriosis, tubal infertility, premature ovarian ageing and immunological infertility tend to be misdiagnosed as UI. In this debate, we present the view that, although scientifically unsatisfying, the diagnosis of UI is sustainable from a clinical and practical perspective. Given our present treatment options, further investigations leading to a more 'accurate' diagnosis is unlikely to change our management in these cases. Scientific curiosity must take second place to a more pragmatic approach, which takes into account the clinical and financial costs of making a more 'accurate' diagnosis.

Keywords: endometriosis; immunological infertility; ovarian ageing; tubal infertility; unexplained infertility

Introduction

Accepted categories of infertility include male factor, tubal disease, anovulation, endometriosis and unexplained infertility (UI) (NICE, 2004). UI is a term used to describe 30–40% of couples (Smith *et al.*, 2003) in whom standard investigations including semen analysis, tests of ovulation and tubal patency have failed to detect any gross abnormality (Crosignani *et al.*, 1993). Its aetiology seems heterogeneous, with suggested potential causes ranging from disturbances in endocrinology, immunology, genetics and reproductive physiology (Pellicer *et al.*, 1998).

The necessity of identifying a specific cause of infertility is linked to the availability of targeted interventions. It is important for couples with UI to receive individualized treatment plans on the basis of their predicted chance of spontaneous live birth, as well as anticipated success rates, costs and complications of treatment. Conception is strongly influenced by female age and the duration of infertility, and treatment independent cumulative live birth rates have been estimated between 33 and 60% at 3 years (Collins *et al.*, 1995).

The Diagnosis of UI

Currently, there are no universally accepted methods for diagnosing UI, which is based on exclusion of the other recognized causes of infertility (Crosignani *et al.*, 1993). Additional investigations have not been shown to improve pregnancy rates (Zayed and Abu-Heija, 1999). The utility of anything other than basic tests of semen quality, ovulation and tubal patency in the diagnosis and management of infertility has yet to be proven (Crosignani *et al.*, 1993; NICE, 2004; Steures *et al.*, 2006). Existing tests of tubal assessment include hysterosalpingography (HSG) and laparoscopy. The diagnostic accuracy of the former has been questioned (Mol *et al.*, 1999) and although laparoscopy is considered to be the gold standard (WHO, 1986), it can miss conditions such as tubal dysfunction or spasm and proximal occlusion (Mol *et al.*, 1999). Hence its cost effectiveness remains to be confirmed (Tanahatoe *et al.*, 2003). Direct and indirect methods for detection of ovulation have been described previously and midluteal progesterone measurement remains the standard test (Crosignani *et al.*, 1993). Strict criteria have been established (Kruger *et al.*, 1986; WHO, 1992) for the diagnosis of semen abnormalities but there may be a degree of overlap between 'normal' and 'abnormal' values. Despite our traditional reliance on these tests to categorize infertility, there is surprisingly little in the literature on their accuracy in terms of prediction of live birth. Taylor and Collins (1992) quantified the degree of accuracy of each test (according to cut-off values used) trying to provide the robust information needed on the contribution of each one to the establishment of UI. Using the Kappa statistic (expressing the overall agreement between a test result and pregnancy), the agreement between the accepted cut-off values for midluteal serum progesterone, sperm concentration, motility and morphology and pregnancy were poor (Kappa ranges 0.18, 0.02–0.24, 0.05 and −0.01–0.22,

respectively), whereas the use of a combination of semen parameters added little to their predictive value. Similarly, laparoscopy and HSG are relatively poor at predicting live birth. Other tests appear to be even less reliable in determining the outcome for any individual couple with infertility (Taylor and Collins, 1992).

The traditional approach towards the diagnosis of UI by means of these basic tests has been questioned (Gleicher and Barad, 2006)—and rightly so. The diagnosis of UI clearly is dependent on the range and accuracy of various investigations used to rule out alternative causes. According to Gleicher and Barad (2006), the availability of such an imprecise diagnostic category encourages clinical lethargy and misdiagnosis—most frequently of the following: endometriosis, mild degrees of tubal infertility, premature ovarian failure and immunological causes.

In this debate, we will refer to four clinical situations specifically mentioned by Gleicher and Barad (2006) in order to determine whether the term UI has any clinical or practical relevance.

Immunological infertility

Autoimmune disease affects up to 20% of men and women in the industrialized world (Cervera, 2001). Much attention has focused on the role of immunological causes in reproductive success, and some evidence has been presented to support the role of autoimmune factors in female infertility (Geva *et al.*, 1995; Roussev *et al.*, 1996; Shatavi *et al.*, 2006; Shoenfeld *et al.*, 2006). These concerns have led to the widespread testing of antiphospholipid, antinuclear, antithyroid and antisperm antibodies, as well as to generalized immune testing. There is little scientific evidence, though, to guide clinical practice in terms of the population to be tested and the nature and timing of the tests. Although preliminary work has shown an association between abnormal immune function and early reproductive failure, more rigorous studies have failed to confirm a causal effect (Kallen and Arici, 2003). For example, most large studies show no benefit following screening for antiphospholipid antibodies (Scott, 2000), nor a positive correlation between immunological factors and infertility (Coulam and Stern, 1992).

Early concerns about an association between peripheral blood natural killer (NK) cells and the outcome of IVF have yet to be confirmed (Somigliana *et al.*, 1999). Women with a peripheral NK cell level $>12\%$ do not have a higher number of previous pregnancy losses or lower pregnancy rates (Thum *et al.*, 2005). Other studies have reported elevated peripheral NK activity in patients with UI as a risk factor for pregnancy failure (Matsubayashi *et al.*, 2001). The inconsistency of the results explains why the new drug therapies have yet to be widely accepted in routine clinical practice. Intravenous immunoglobulin, for example, has not been shown to improve the live birth rates in couples with IUI and repeated unexplained IVF failures (Stephenson and Fluker, 2000). It is therefore logical to question the purpose of making a conclusive diagnosis in the absence of any targeted treatment strategies. In men, many of the treatment options for infertility of immunological origin [immunosuppression, intrauterine insemination (IUI) and conventional *in vitro* fertilization (IVF)] have been superceded by intracytoplasmic sperm injection (McLachlan, 2002).

Mild tubal disease

As diagnostic tests, HSG and laparoscopy have some limitations in terms of accuracy in assessing tubal patency and function (Crosignani *et al.*, 1993; Evers, 2002). Although the use of these tests as predictors of pregnancy have led to discordant results (Mol *et al.*, 1999), they are unlikely to miss many women with blocked tubes who need urgent referral for IVF. HSG will fail to identify some women with minor degrees of peritubal disease, who might have been correctly 'diagnosed' by laparoscopy, although the extent to which mild adhesions around a patent tube can affect fertility is uncertain. Mol *et al.* (1999) reported for HSG a sensitivity of 0.81 and a specificity of 0.75, in identifying tubal occlusion detected at laparoscopy. But in terms of predicting pregnancy, laparoscopy was more reliable (fecundity rate ratios of 0.38 and 0.19 when a one- and two-sided occlusion appeared, respectively) compared with HSG, even if not considered the ultimate solution, whereas the agreement of the two techniques was moderate (expressed by a kappa statistic of 0.42) (Mol *et al.*, 1999). In women with patent tubes, it would be perfectly reasonable to adopt an expectant approach (taking into account age and duration of subfertility) before considering IVF. Thus, inability to exclude a diagnosis of subtle tubal defects is unlikely to change the overall plan of management in this population.

Endometriosis as a cause of UI

In the absence of a detailed laparoscopic examination of the pelvis, endometriosis could be misdiagnosed as UI (Olive and Schwartz, 1993). Severe endometriosis has been shown to affect the outcome of infertility. In a meta-analysis of 22 studies, pregnancy rates were found to be lower in women with endometriosis compared with controls (women with tubal disease) (Barnhart *et al.*, 2002). Fertility treatment in the presence of severe endometriosis is associated with lower success rates compared with mild disease (Guidice and Kao, 2004) due to a disturbed milieu within the pelvis (Arici *et al.*, 1996).

The management of infertility related endometriosis depends on the severity of the condition. By and large, interventions for minimal/mild endometriosis are not dissimilar to those used for UI, i.e. superovulation/IUI and IVF (NICE, 2004). This calls into question the justification for diagnosing minimal and mild endometriosis separate from UI (Evers, 2002). Medical treatment is ineffective for endometriosis-associated subfertility (Hughes *et al.*, 2003). Potential improvement in AFS scores does not justify costs, adverse effects and lost opportunities for conception associated with medical treatment (Yap *et al.*, 2004). Laparoscopic resection or ablation of lesions in minimal and mild endometriosis led to contradictory results, in terms of improvement of fertility (Marcoux *et al.*, 1997; Parazzini, 1999). The findings of Marcoux *et al.* (1997) suggest improvement of chances of pregnancy following laparoscopic treatment of mild endometriosis, but the

benefits must be balanced against the invasive nature of the procedure. Instead, expectant management, especially if endometriosis is mild and discovered as an incidental finding followed, if unsuccessful, by superovulation/IUI and IVF is the accepted management (NICE, 2004). Data from national registries show no difference in IVF outcomes in women with and without endometriosis (Templeton *et al.*, 1996).

A multivariate analysis showed that endometriosis does not affect cumulative conception rates in the absence of anatomical distortion of the pelvis (Olive and Schwartz, 1993). In fact, a diagnosis of moderate/severe disease is likely to strengthen the decision to go for IVF.

Advanced female age and UI

A tendency to delay childbearing for social reasons has resulted in increasing numbers of women seeking infertility treatment at an advanced age. The ageing ovary shows high rates of follicular atresia and poor follicular growth, which has been referred to as 'poor ovarian response'. It is currently unclear whether an effective diagnostic test for poor ovarian reserve exists (Broekmans *et al.*, 2006), and the management strategy for this condition remains speculative (Tarlatzis *et al.*, 2003). In the absence of reliable and accurate markers for ovarian reserve (Broekmans *et al.*, 2006), older women will be offered the same treatment options, such as controlled ovarian stimulation with IUI, IVF, and ultimately oocyte donation. It is true that in these women IVF is not only 'ultimate therapeutic modality, but also the ultimate diagnostic test' (Gleicher and Barad, 2006). It is questionable whether formal identification of women with poor ovarian reserve could improve their chances of live birth.

Further considerations

Most clinicians would agree that the fundamental reason for making an accurate diagnosis is to be able to offer a prognosis and devise a treatment plan. Data from large national studies show that the independent effect of crucial prognostic factors such as female age, parity and duration of infertility are dominant when it comes to predicting live birth (Templeton *et al.*, 1996). Recent trials have questioned the validity of many of the first line conventional treatments for UI before IVF is contemplated. Most of these have included women with mild endometriosis and mild male factor infertility as well (Steures *et al.*, 2006; Bhattacharya *et al.*, 2006).

Reduction in treatment options has rekindled interest in expectant management in cases where the expectation of spontaneous pregnancy is high. Alternatively, regardless of diagnosis, the threshold for IVF is low in couples with prolonged infertility and advanced female age (Steures *et al.*, 2006). In making such decisions, it can be argued that it is unnecessary to go to extreme lengths in the quest of an 'accurate' diagnosis.

Conclusion

While scientifically unsatisfying, the diagnosis of UI appears sustainable from a clinical and practical perspective. Given the paucity of effective targeted interventions for conditions like mild endometriosis, minor degrees of tubal disease, immunological causes and poor ovarian reserve, better diagnosis cannot lead to a radical improvement of the outcome. It would be more practical for patients in the above subgroups to be treated similarly to UI, taking age and duration of infertility into consideration.

Substitution of the term 'unexplained' with 'undiagnosed' infertility as suggested by Gleicher and Barad (2006) seems to be little more than an exercise in semantics. In spite of intensive investigations, some cases of infertility will continue to remain 'undiagnosed' or 'unexplained'. It may not be in the best interests of patients to be subjected to invasive and expensive tests in order to satisfy scientific curiosity, where new information does not directly contribute to better clinical decision making.

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