

DEBATE

Investigation of the infertile couple

Investigation of the infertile couple in the era of assisted reproductive technology: a time for reappraisal

Juan Balasch¹

¹To whom correspondence should be addressed at: Institut Clinic of Gynecology, Obstetrics and Neonatology, Faculty of Medicine-University of Barcelona, Hospital Clínic-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), C/Casanova 143, 08036-Barcelona, Spain. E-mail: jbalasch@medicina.ub.es

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At present, several of the elements in widespread use in basic infertility testing are in dispute, marked variability exists in the work-up among specialists, and practice patterns are influenced both by modern assisted reproductive technologies (ART) and the increasing age of couples seeking help for infertility. This article is intended to stimulate the debate on a possible (lack of) usefulness of conventional methods of infertility evaluation in relation to both the modern techniques of assisted reproduction and the woman's age.

Key words: aged women/assisted reproduction/infertile couple/infertility evaluation/practice patterns

Introduction

Only 40–45 years ago, infertility was a non-topic. Little was known scientifically or medically, and the topic was hardly ever discussed socially. It was then considered proper not to inform the patient of a serious diagnosis and infertility was commonly considered untreatable. Times have changed and the problem of infertility in Western societies has increased in several ways over the past 15–20 years (Jones and Toner, 1993; Lincoln, 1995). Firstly, there are more infertile women in the population. Secondly, a larger proportion of infertile couples now seek treatment. Greater numbers seeking help, however, should not be interpreted as evidence that infertility rates are rising (Mosher and Pratt, 1991). Greater numbers seeking help are evidence that more help is available, more couples know that help is available, and a big cohort is at the age where they are most likely to use that help. Indeed, most women are currently delaying childbearing to an age where they are more likely to encounter problems having a child. In response to a dramatically increased demand for infertility investigations, fertility service centres have developed and expanded, together with the use of assisted reproductive

technologies (ART) (Jaffe and Jewelewicz, 1991; Mosher and Pratt, 1991; Jones and Toner, 1993; Hedon *et al.*, 1995).

A remarkable feature of ART is that they have transformed the treatment of infertility but also its diagnosis (Blackwell *et al.*, 1987; Karande *et al.*, 1999; Johnson *et al.*, 2000). Increasingly, with the advances made in the ART, there is a move away from a 'diagnostic work-up' towards a 'prognosis-orientated approach' to the investigation and treatment of infertility. Unfortunately, however, ART are sometimes used to treat incompletely-evaluated patients; women are recommended to proceed to ART following an accelerated and often incomplete work-up. Because of the remarkable progress in the availability and success of IVF-embryo transfer, it has been assumed that more liberal use of this and other ART is warranted as part of routine infertility treatment. Consequently, irrespective of the fact that certain conditions dictate the use of advanced therapy early in the work-up, IVF increasingly is being used as the prime intervention in newly established infertility approaches.

The improvements observed in the pregnancy rates associated with IVF, however, could be partly the consequence of the patient selection process. As couples with infertility undergo ART earlier, the patient population is changed to one with a higher chance of success. Patients for whom other treatments have failed have a lower chance of success. The rising pregnancy rates for IVF therefore may reflect an evolving change in patient selection criteria and not just an improvement in ART. Nevertheless, it remains to be seen whether certain groups of patients, even those who have no obvious contra-indication to the use of standard infertility treatment algorithm, may benefit from first-line treatment with IVF (Karande *et al.*, 1999).

On the other hand, the basic infertility investigation of the 1990s has modified and expanded the traditional work-up (Campana *et al.*, 1995) and so care must be taken to avoid exploitation of the infertile couple with expensive, unnecessary tests, procedures, and treatments (Jaffe and Jewelewicz, 1991; ESHRE Capri Workshop, 1996). It can be argued that performing comprehensive investigations may explain or define causes of otherwise unexplained infertility, but when many tests are carried out that are independent or partially independent, then the chances of encountering a false-positive result increases exponentially (Hatasaka *et al.*, 1997; Zayed and Abu-Heija, 1999).

Against the above background, the question arises as to which should be, at present, procedures for the investigation of the infertile couple. Traditionally, the cornerstones of assessing an infertile couple have been grouped into five standard testing categories. These include: semen analysis; assessment of ovulation (usually by endometrial biopsy);

evaluation of uterine architecture and tubal patency; the post-coital test (PCT); and laparoscopy (American Fertility Society, 1992; Rowe *et al.*, 1993). Despite the basic work-up outlined by the American Fertility Society (1992) and the World Health Organization (WHO) guidelines (Rowe *et al.*, 1993), a lack of agreement exists among trained fertility subspecialists with regard to the diagnostic tests to be performed and their prognostic utility as well as criteria for normality. Thus, a questionnaire survey among the teaching departments of obstetrics and gynaecology in Western Europe revealed only weak adherence to the WHO recommendations for the standard investigation of the infertile couple with large differences among countries in the preferred standard testing methods. From this study it was concluded that fertility investigations are based more on tradition and personal preference, than on the demonstrated usefulness of its components (Helmerhorst *et al.*, 1995). This agrees with the findings of similar studies performed among the US board-certified reproductive endocrinologists which demonstrated that, although most trained specialists agree on the major areas of the performance of infertility testing as outlined by the American Fertility Society (1992), there was significant variability in details of the performance of most testing (including both criteria for normality and the interpretation of results), especially with respect to physician sex, age, type of practice, and geographic location. There was even less agreement with regard to additional modes of testing (e.g. hormonal testing, use of pelvic ultrasounds, hysteroscopy, cervical cultures, antisperm antibody) besides those five 'traditional' infertility tests (Glatstein *et al.*, 1997, 1998).

At present, agreement regarding standard infertility testing is not readily obtained because of several reasons. Firstly, different views about the value of traditional diagnostic tests and marked variety of clinical experience exist. Secondly, the prognostic information provided by more recent 'additional' infertility tests aimed to obtain a more comprehensive assessment of sperm, cervical, endometrial and tubal functions, seems neither significant nor cost-effective. Thus, the usefulness of such extended evaluation remains highly controversial. These aspects have been widely discussed in the literature (Jaffe and Jewelewicz, 1991; ESHRE Capri Workshop, 1996) and they are beyond the scope of the present report. In this respect, it is to note that the ESHRE Capri Workshop (1996) stressed that although some believe that any abnormal diagnostic test result defines a cause of infertility, it is more probable that abnormal test results define a cause of infertility only when treatment of this cause enhances fecundability in comparison with no treatment. After a critical review of the literature, the group concluded that abnormal tests that have an established correlation with impaired fecundability are semen analysis, tubal patency by hysterosalpingography (HSG) or laparoscopy, and laboratory assessment of ovulation. In addition, the group stressed that since tubal patency may not be the only cause of infertility, laparoscopy may also help to detect other factors, e.g. endometriosis, adhesions (ESHRE Capri Workshop, 1996).

Finally, a most interesting point deserves discussion. It refers to how practice patterns in infertility may change as new ART become integrated into the procedures available to infertility

practitioners and the number of infertile women in the advanced reproductive age group is increasing. Whilst semen analysis seems a universally accepted test (Helmerhorst *et al.*, 1995; Glatstein *et al.*, 1997) for which it is claimed that prospective studies have demonstrated a significant relationship between assessment of traditional semen parameters and the outcome of ART, particularly IVF and intrauterine insemination (IUI) (Barratt, 1997; Barratt and St John, 1998), different questions can be raised regarding other traditionally accepted infertility tests with a view to ART.

This article is presented to stimulate the debate on the possible (lack of) usefulness of conventional methods of infertility evaluation in relation to both the modern techniques of ART and the age of the woman.

Post-coital test (PCT)

According to a recent study (Oei *et al.*, 1995) which assessed differences in opinion and practice with regard to the PCT in 16 European countries, this test is rated as one of the least useful of the standard fertility investigations. However, it is still widely applied in the institutions (92% overall, and routinely in 68% of departments) where future generations of fertility specialists are taught. The authors stressed, however, that divergence in practice and opinion is wide enough to question whether infertile couples are better off with than without the test (Oei *et al.*, 1995). In fact, evidence-based medicine seems to be against the prognostic value of the PCT (Griffith and Grimes, 1990; Helmerhorst *et al.*, 1997; Oei *et al.*, 1998) although, on the basis of observational studies and clinical experience, a number of authors claim a strong association between the PCT results and pregnancy rates (Hull *et al.*, 1982; Eimers *et al.*, 1994; Hall and Montgomery Rice, 1995; Cohlen *et al.*, 1998; Hull and Evers, 1998). It should be stressed that evidence-based medicine is about integrating individual clinical expertise and the best external evidence, but clinical skill is essentially derived from experience and is expressed as judgement in decision-making (Sackett *et al.*, 1996; Smith, 1996). However, the variation in the ways in which different individuals interpret experience and formulate judgements renders this aspect difficult to expose to 'big statistical ways of thinking' (Smith, 1996).

Apart from problems with standardization and interpretation of the test, a well-timed mid-cycle PCT permits an assessment of spermatozoa-mucus interaction which, interestingly, has been shown to be related to sperm fertilizing ability (Hall and Montgomery Rice, 1995) and results of human IVF in couples with unexplained infertility (Hull *et al.*, 1984; Balasch *et al.*, 1989). According to Hull and Evers (1998), the PCT is of predictive value for natural conception mainly in couples with <3 years duration of otherwise unexplained infertility, although it remains predictive for fertilization *in vitro* and therefore for choice of assisted conception method, even after prolonged infertility. This is to be noted considering that to date, the assessment of sperm function in a clinical programme has produced disappointing results and a cost-effective, widely available, clinically relevant sperm function test is not available (Barratt and St John, 1998). On this basis, some authors start

with IVF to provide diagnostic information about fertilizing ability before considering the other treatments, e.g. IUI, if necessary (Hull *et al.*, 1992).

In fact, the initial indications for IUI were failure of spermatozoa to penetrate cervical mucus and male infertility. During the past decade, the indications for IUI have been liberalized and now it is frequently employed in conjunction with the woman's use of gonadotrophins. Cervical infertility (as defined by repeatedly abnormal PCT) is a very clear-cut indication for carrying out IUI combined with gonadotrophin ovarian stimulation (Hull, 1992; Edwards and Brody, 1995; Forti and Krausz, 1998) which is the favourite therapy among specialists (Oei *et al.*, 1995; Speroff *et al.*, 1999). This adds further to the debate surrounding the PCT when considering its frequent use, cost, and the investment of time for both physician and patient in relation to its potential to alter patient management in a meaningful fashion (Bush *et al.*, 1997). Thus, a newer argument raised against use of the PCT is that widespread use of IUI combined with ovulation stimulation has made the assessment of sperm-cervical mucus interactions merely an academic exercise. So, whether the PCT is normal or abnormal, the treatment is the same (Speroff *et al.*, 1999). In fact, combined IUI and ovulation stimulation using gonadotrophins or, alternatively, IVF may succeed in cervical infertility as well as they do for unexplained infertility (Hull, 1992). IUI with ovulation, however, is hazardous in terms of multiple pregnancy and the monthly fecundity rate is generally poor (Guzick *et al.*, 1999; te Velde and Cohlen, 1999).

Laparoscopy

Traditionally, laparoscopy has been the final diagnostic procedure used in infertility investigations. However, as the success rates with IVF improve, clinicians increasingly believe that turning to the ART is appropriate, even without laparoscopy (Speroff *et al.*, 1999). Also, with the option of IVF, it is often hard to persuade a woman with a normal HSG to undergo an invasive procedure, e.g. laparoscopy. It has been stressed that these women often prefer to have IVF, with a good chance of pregnancy (Hovav and Hornstein, 1999). Transvaginal hydrolaparoscopy, which is performed under local anaesthesia as an office procedure for infertility investigation, may represent a new tool in this regard (Gordts *et al.*, 1998a,b; Campo *et al.*, 1999).

A number of apparently normal infertile patients undergoing laparoscopy will have pelvic pathology, usually endometriosis or adnexal adhesions. It has been claimed that adhesiolysis has the best results if the adhesion is the only factor responsible for the infertility, with no existing differences between adhesiolysis by laparoscopy or by laparotomy and so laparoscopy must be preferred (Posaci *et al.*, 1999). However, others stress that in the presence of tubal patency pelvic adhesions are of lesser significance and thus having a laparoscopy should be determined by patient preference rather than the clinician's wish (Collins, 1998).

Salpingectomy prior to IVF in patients with hydrosalpinx can improve pregnancy rates. This is supported by two recent meta-analysis aimed to evaluate differences in pregnancy rates

after IVF in tubal infertility with and without hydrosalpinx (Zeyneloglu *et al.*, 1998; Camus *et al.*, 1999). Both studies concluded that hydrosalpinx present during IVF/embryo transfer is associated with a reduced chance of implantation and an increased risk of pregnancy loss. In addition, a randomized multicentre trial in Scandinavia on salpingectomy prior to the first cycle of IVF/embryo transfer (Strandell *et al.*, 1999) indicated that clinical pregnancy rates per included patient were 36.6% in the salpingectomy group and 23.9% in the non-intervention group ($P = 0.067$) and the ensuing delivery rates were 28.6 and 16.3% ($P = 0.045$). Finally, patients with a hydrosalpinx have shown significantly lower implantation rates and significantly higher miscarriage and ectopic pregnancy rates than normal controls in donor oocyte cycles (Cohen *et al.*, 1999).

Despite this apparent evidence, thoughtful opinions have claimed against indiscriminate 'prophylactic' salpingectomies before IVF on women with hydrosalpinx (Aboulghar *et al.*, 1998; Bloechle, 1999; Lass, 1999; Sharara, 1999). According to this view and supported by results in the multicentre Scandinavian study (Strandell *et al.*, 1999), only a subset of patients would benefit most from surgery: women having ultrasound visible hydrosalpinx (in particular those affected bilaterally) with reflux of fluid into the endometrial cavity. On the other hand, from an ovarian perspective, salpingectomy, not properly performed close to the tube, may disrupt the normal blood flow to the ovary (Lass, 1999). Thus, in women who had had unilateral salpingectomy prior to IVF/embryo transfer, there were fewer follicles and, consequently, fewer oocytes were retrieved from the side of operation in comparison with side with intact adnexa (Lass *et al.*, 1998). Additional recent reports demonstrating that hydrosalpinx fluid does not adversely affect the normal development of human embryos and implantation *in vitro* (Granot *et al.*, 1998; Strandell *et al.*, 1998) but rather enhances human trophoblast viability and function *in vitro* (Sawin *et al.*, 1997), add further controversy to the subject.

In a study where the standard infertility tests were performed on both fertile and infertile couples, endometriosis and tubal damage were reported as the only infertility factors occurring significantly more frequently ($P < 0.05$) among infertile than fertile couples (Guzick *et al.*, 1994a). Other prospective studies, however, reported that the prevalence of minimal to mild endometriosis was similar in fertile and infertile women (Rawson, 1991; Balasch *et al.*, 1996) although immunological mechanisms of endometriosis-associated infertility existing in infertile women with endometriosis are lacking among fertile women with endometriosis (Martinez-Román *et al.*, 1997a,b).

The medical treatment of endometriosis does not improve pregnancy rates (Hughes *et al.*, 1998), and intra-operative destruction of minimal to mild lesions has only a small effect (Marcoux *et al.*, 1997), if any (Gambone and DeCherney, 1997; Bérubé *et al.*, 1998; Tummon *et al.*, 1998; Gruppo Italiano per lo Studio dell'Endometriosi, 1999), on fecundity. On the contrary, different studies have indicated that prolonged treatment with gonadotrophin-releasing hormone (GnRH) analogue before ovarian stimulation for IVF or gamete intra-Fallopian transfer (GIFT) provides better chances of success

in patients with endometriosis (Remorgida *et al.*, 1990; Dicker *et al.*, 1992; Guzick *et al.*, 1994b; Marcus and Edwards, 1994).

The above notwithstanding, a recent study (Aytoz *et al.*, 1998) reported that when sperm morphology was evaluated according to Kruger's strict criteria (Kruger *et al.*, 1988), the probability of finding pathology on laparoscopy in the normal male group (16.7%) was statistically higher than that in the group with severely abnormal spermatozoa (1.8%; $P < 0.01$). The authors concluded that there is no need to perform a preliminary diagnostic laparoscopy in the female partner if a full work-up is normal in couples with severe male-factor infertility willing to undergo intracytoplasmic sperm injection (ICSI) (Aytoz *et al.*, 1998). In couples with severe male-factor infertility, the woman may indeed be fertile despite having minimal/mild endometriosis. This is well exemplified by early studies examining fecundity in women undergoing donor insemination for an absolute male factor (Portuondo *et al.*, 1983; Rodriguez-Escudero *et al.*, 1988). Endometriosis as a paraphysiological condition, and endometriosis as a 'disease' are now well recognized (Rawson, 1991; Vercellini and Crosignani, 1993; Thomas, 1994; Balasch *et al.*, 1996; Martinez-Román *et al.*, 1997a). This concept should also apply to studies investigating the possibility that the presence of endometriosis in the female could impair the overall results of the ICSI process in a couple. A recent report (Minguez *et al.*, 1997) suggested that potential defects in the process of oocyte activation in endometriosis patients could be overcome by the ICSI procedure. Again, however, this study was based on severe-male factor infertile couples and thus we do not know the 'level' of female fertility.

Endometrial biopsy

While it is known that endometrial receptivity during the implantation window is crucial to successful conception, no histological or biochemical assessment of endometrial responses has been reliably associated with conception (Balasch *et al.*, 1992a; Edwards, 1995; Creus *et al.*, 1998; Giudice, 1999). On the other hand, assessment of endometrial function during a spontaneous cycle previous to IVF seems irrelevant considering the ovarian stimulation associated with ART. Thus, new markers able to identify a receptive uterus prospectively by a non-invasive method are urgently needed in order to improve efficiency and success rates following ART. In this respect, the role of ultrasonography seems promising but its definite value still remains to be proved by controlled prospective studies (Friedler *et al.*, 1996). It is possible that three-dimensional ultrasound systems may provide improved spatial evaluation of pelvic organs and thus better objective parameters by which to predict endometrial receptivity (Raga *et al.*, 1999).

Hysterosalpingography

HSG is widely used as first-line approach to assess the anatomy of the uterus and the patency of the Fallopian tubes in infertility evaluation. The relative merits of HSG and laparoscopy in screening for tubal factors have been discussed for >20 years, but no study has used formal randomization procedures to

establish which of these two methods is the most deserving of being incorporated in a standard infertility work-up (Helmerhorst *et al.*, 1995). More recently, hysteroscopy has been added to the controversy and while some authors consider that hysteroscopy is a technique that complements HSG (Speroff *et al.*, 1999), others claim that HSG or one of the newer alternative techniques to evaluate tubal morphology and function should supplement the hysteroscopic assessment (Shushan and Rojansky, 1999). In the women scheduled for IVF or ICSI, however, tubal status, beyond the presence of hydrosalpinges, is of no concern. The point is then whether sonohysterography which is a non-invasive method (Goldberg *et al.*, 1997; Gronlund *et al.*, 1999) may suffice for evaluating the uterine cavity in patients undergoing ART. Preliminary data (Alatas *et al.*, 1998) suggesting that in comparison with HSG, evaluation of the uterine cavity with sonohysterography does not compromise pregnancy rates in such patients, deserve further study.

Infertility evaluation in older couples

As discussed above, delayed childbearing is becoming increasingly common in Western society and thus infertile women who are in their late 30s or early 40s now make up the majority of patients in many practices. This fact together with decline of fertility with age have led to an increased interest in the reproductive capacity of those aged women and a search for treatment options that may improve their fertility.

Age (up to 64 years) does not affect sperm characteristics or its ability to fertilize human oocytes (Gallardo *et al.*, 1996), but because age is an important determinant of female fertility, evaluation and therapy should not be deferred in older women. For infertile women of advanced reproductive age, however, the decreased emphasis on diagnosis and rapid movement toward ART seem especially manifest. Thus, recommendations for older couples have included that: (i) there is no time to waste; and (ii) serious consideration should be given to an early resort to hormonal stimulation for both oocyte response and support of the endometrium (Speroff, 1993; Speroff *et al.*, 1999). This would imply that the increase in infertility experienced by these couples is caused by ageing gametes or abnormal folliculogenesis and then, the standard infertility tests would not detect any abnormalities. However, another scenario could be present: in relatively older couples an evaluation would find more diseases known to cause infertility. The female partner would have had a longer exposure for development of pelvic adhesions, obstructed tubes, and endometriosis; because she would have lost a majority of the primordial follicles, more ovulatory problems would be detected (Miller *et al.*, 1999). Two studies (Balasch *et al.*, 1992b; Miller *et al.*, 1999) aimed to determine infertility factors in women of advanced reproductive age concluded that there is no unique pattern of infertility diagnoses in such patients. Interestingly, the only statistically significant finding in both studies was that older women had fewer ovulatory problems; in addition, tubal factor was the commonest detected female infertility cause in the older groups. However, despite that it has been documented that women suffering from

polycystic ovary-like conditions gain regular menstrual cycles when ageing (Elting *et al.*, 2000), this does not imply an improvement of their fecundability.

The above notwithstanding, many older infertile women having regular menses will have an impaired response to ovarian stimulation for ART because of so-called occult ovarian failure which is associated with elevated basal FSH serum concentrations (Cameron *et al.*, 1988). Also, it has been reported that impaired ovarian function may be a contributing factor to infertility in women with pelvic adhesions who will respond less well to stimulation at IVF (Bowman *et al.*, 1993). Considering that the analysis of the influence of women's age on the results of IVF shows a marked decline in success rates at 35 years (Piette *et al.*, 1990; Tan *et al.*, 1992; Pouly *et al.*, 1995), while an excellent success rate (45% pregnancy rate with a mean interval between the operation and pregnancy of 5.5 months) might be obtained by the reversal of tubal ligation in women >40 years of age (Trimbos-Kemper, 1990), the question arises whether any adverse effect of ageing becomes evident earlier for ART success than in the field of natural fertility (including post-surgical fecundity). The answer to this question would have important implications for both diagnosing and treating infertile women.

Conclusions

In conclusion, several of the elements in widespread use in basic infertility testing are in dispute, marked variability exists in the work-up among specialists, and practice patterns are being influenced by both modern ART and advanced age of couples seeking help for infertility. With marked discrepancies in the literature regarding infertility evaluation it is difficult to compare ART results according to different causes of infertility. Clearly, it is time for reappraisal.

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