Treatment of male infertility due to sperm surface antibodies: IUI or IVF?

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This prospectively designed study was aimed at comparing the results of two different treatment protocols in 29 infertile couples with proven male immunological infertility, i.e. a positive (>50%) mixed antiglobulin reaction (MAR) test (IgG and/or IgA). In the first protocol (group I, n = 14) couples were treated with ovarian stimulation/intrauterine insemination (IUI), followed by in-vitro fertilization (IVF) if no pregnancy occurred after three IUI cycles. In the second protocol (group II, n = 15), patients were treated with IVF as a first choice procedure. The decision to follow protocol 1 or 2 was made by the couples after information about financial costs and expected success rates (according to the literature) for both treatment options. In group I, nine patients (64.3%) conceived after a maximum of three IUI cycles whereas seven patients (46.6%) of group II became pregnant during the first IVF cycle. The take-home baby rate per started IUI or IVF cycle was 27.3% (9/33) and 44.4% (16/36) respectively with a take-home baby rate of 64.3% after three IUI cycles and 93.3% after three IVF attempts. To conclude, both IUI and IVF yielded unexpectedly high pregnancy rates in this selected group of patients with long-standing infertility due to sperm surface (predominantly IgG) antibodies. Since cost benefit analysis comparing superovulation IUI with IVF may favour a course of four IUI cycles, we advocate superovulation IUI as the first line therapy in male immunological infertility.

Key words: antisperm antibodies/intrauterine insemination/in-vitro fertilization/male infertility

Introduction

The clinical significance of antisperm antibodies (ASA) in male infertility remains unclear (Rümké, 1980; Husted and Hjört, 1975; Barratt et al., 1992; Jarow and Sanzone, 1992) and the importance of circulating ASA is probably low (Critser et al., 1989; Eggert-Kruse et al., 1989; Marshburn and Kutteh, 1994). However, most studies demonstrate a clear association between sperm surface antibodies and the fertility potential of the male (Hjört and Hansen, 1983; Adeghe et al., 1988; Hammitt et al., 1988; Matson et al., 1988; Acosta et al., 1994) although Barratt et al. (1992) demonstrated a lack of correlation between low (<10%) and moderate (<50%) ASA positive binding cases and the probability of conception or the time to conception.

ASA found in semen are usually immunoglobulins of the IgG or IgA isotype that are directed to various sites of the spermatozoa, i.e. head, midpiece, tail, or combinations thereof (Peters and Coulam, 1992). IgGs in semen are mostly regarded as transudates from the systemic circulation via the prostate gland, whereas IgA is usually (60–90%) secretory in type, suggesting intratesticular and/or epididymal synthesis (Adeghe, 1992). The binding of these antibodies can be directed toward carbohydrate or peptide moieties of sperm antigens, but the binding can also occur via Fc receptors (Allen and Boune, 1978; Isojima, 1988). In general, tail-directed ASA tend to influence and disturb sperm progressive motility, whereas head-directed ASA may alter fertilization by occluding binding sites for zona pellucida binding (Bronson et al., 1984) or by affecting motility parameters, e.g. the amplitude of lateral head displacement (Zouari et al., 1993). The acrosome reaction, another crucial step in human sperm function, can also be altered by ASA (Lansford et al., 1990).

From a physiological point of view, immunological infertility due to sperm surface antibodies can result from the effect on sperm transport, the destruction of gametes, acrosome reaction abnormalities, by inhibition of sperm–zona pellucida binding or by prevention of embryo cleavage and early development of the embryo (Bronson et al., 1984; Shushan and Schenker, 1992).

Surprisingly, spermatogenesis is apparently not affected by the presence of IgG or IgA ASA since sperm density and/or morphology are not influenced by the presence of these antibodies (Haas et al., 1983; De Almeida et al., 1991).

Concerning therapy, the use of antibiotics is only worthwhile and the importance of circulating ASA is probably low (Critser et al., 1989; Eggert-Kruse et al., 1989; Marshburn and Kutteh, 1994). However, until now no prospective study has been published comparing the effectiveness of the first line IUI approach.
versus IVF for male immunological infertility. The objective of our prospective study was to compare success rates after two different treatment protocols for couples with male immunological infertility, namely IUI superovulation versus IVF.

Materials and methods

Patients

During a 60 month period, from January 1991 until December 1995, 29 couples in our infertility programme were selected for this study. Only patients with a history of infertility for at least 2 years and without any major female factor such as tubal factor infertility and/or major anovulatory disorders were included. Anovulation was confirmed by ultrasound, basal body temperature and/or hormonal abnormalities (oestradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin and progesterone). As part of our routine infertility investigation, all female partners had undergone a laparoscopy, a hysterosalpingography, an endocervical examination (oestradiol, LH, FSH, prolactin and progesterone) and a local (postcoital test, cervical mucus) and systemic (titre of circulating serum ASA) immunological examination. Patients with anovulation due to polycystic ovary syndrome were also excluded from the study. To detect ASA in semen samples of both men and women, we used an enzyme-linked immunosorbent technique (ELISA, Eurogenetics, Tessenderlo, Belgium).

The male factor was evaluated by basic semen analysis of at least two samples and the mean of these was used in this study. Special attention was given to the volume of the ejaculate, pH, sperm concentration, progressive motility, viability, 24 h survival and bacteriology following the WHO guidelines (WHO, 1987), except for morphological examination, for which strict criteria were used (Kruger et al., 1986). In our search for seminal ASA, we used the modified mixed antiglobin reaction (MAR) for immunoglobulin G and A (SpermMar®, Fertipro, Lotenhulle, Belgium) (Jager et al., 1978; Andreou et al., 1995). The IgA assay became available only in 1992, therefore some of our patients could not be tested for IgA (indicated as not done (nd) in Table II). The method of MAR testing did not change during the study period and an intra-laboratory study on the reproducibility of these tests showed very low intra- and inter-observer variability (Pearson correlation coefficient 0.90 or more, data not published).

Only men with a moderate to severe (binding to 50–100% of spermatozoa) positive mixed antiglobulin reaction (MAR, IgG and/or IgA) on two or more consecutive semen samples (interval: at least 1 month) were selected. If the test showed binding of >50% motile spermatozoa, the different sites of binding (head, midpiece and/or tail) were specified. Patients were also MAR positive (>50% in all examined treatment cycles. Positive agglutination was recorded if present. After selection of positive samples, semen was also examined after washing (swim-up procedure or miniPercoll) and, if >0.5 × 10⁶ motile spermatozoa were recovered, two treatment options were offered to the patients: (i) a maximum of three superovulation/IUI cycles followed by IVF or (ii) IVF (maximum three cycles). Before making their decision, patients were informed about the financial costs (in favour of IUI) and the expected success rate (in favour of IVF), according to the literature. Since we performed a prospective study comparing success rates of repetitive IUI versus IVF, only patients without tubal factor infertility were included in the study.

A total of 14 couples decided to start with IUI (group I), while the remaining 15 couples underwent IVF as the first treatment (group II).

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A total of 14 couples decided to start with IUI (group I), while the remaining 15 couples underwent IVF as the first treatment (group II).

**Table I.** Comparison of duration of infertility, female age and sperm antibody titre (IgG and IgA defined as % of motile sperm bound) in group I versus group II

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<th>Group I (n = 15)</th>
<th>Group II (n = 14)</th>
<th>P value</th>
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<tr>
<td>Duration of infertility (months)</td>
<td>42.6 ± 23.9</td>
<td>25–96</td>
<td>42.1 ± 26.8</td>
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<td>Female age (years)</td>
<td>29.4 ± 2.7</td>
<td>25–34</td>
<td>29.6 ± 4.0</td>
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<td>MAR IgG (%)</td>
<td>78.0 ± 17.6</td>
<td>55–100</td>
<td>77.2 ± 17.4</td>
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<td>MAR IgA (%)</td>
<td>29.6 ± 30.4</td>
<td>0–74</td>
<td>26.1 ± 25.1</td>
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NS = not significant, Student’s t-test

**In-vitro fertilization procedure**

For ovulation induction, two different regimens were used. In our first protocol (1991–1992) we used the combination of clomiphene citrate 50 mg (Clomid®, Merrell Dow, Zaventem, Belgium or Pergo-time®, Serono, Brussels, Belgium) and 75 units of human menopausal gonadotrophin (HMG; Humegon®; Organon, the Netherlands, or Pergonal®; Serono, Italy) daily on days 5–9. From the 10th day of the cycle all patients attended our clinic daily for follicular ultrasonography (Aloka®, Biomedic Belgium, Mechelen, Belgium; endovaginal probe, 5 MHz) and serum LH, progesterone and oestradiol determinations. Additional HMG (75 or 150 units) was given during the next 1–4 days depending on the follicular growth and oestradiol concentrations. HCG (5000 units, Profasi®; Serono, or Pregnyl®; Organon) was administered when the average diameter of the dominant follicle was ≥19 mm, in the presence of an adequate serum oestradiol response (≥800 pg/ml) and a serum oestradiol ≥400 pg/ml/follicle with a diameter ≥15 mm.

In the second protocol (1993–1995) a combination of luteinizing hormone-releasing hormone (LHRH) analogues (Buserelin®, Hoechst, Brussels, Belgium; nasal spray 800 µg/day) and HMG was used starting on day 2 of the cycle (short regimen). HCG was given when the above mentioned criteria regarding diameter of the dominant follicle and serum oestradiol concentration were met. The two different stimulation protocols were equally distributed in both study groups.

All oocytes were retrieved under vaginal ultrasound guidance, 36 h post-HCG. Oocytes were categorized into the following classes: post-mature metaphase II, metaphase II, mature metaphase I and prophase I.

**Insemination procedure**

In our IUI programme, all patients received follicular stimulation medication. The first choice treatment was the clomiphene citrate–human chorionic gonadotrophin (CC-HCG) regimen. A daily dose of 50 mg was given for 5 days starting on day 3–5 of the cycle. In those patients with a history of clomiphene resistance we used 75 units of HMG daily on days 5–9 (HMG-HCG regimen). At the 10th day of the cycle, all patients attended our clinic for follicular ultrasonography and serum oestradiol determination. Additional HMG (75 or 150 units) was given during the following days if the ovarian response was insignificant. In both regimens, HCG 5000 units were given when the average diameter of the dominant follicle was ≥19 mm. In all IUI cycles, two intrauterine inseminations were performed on two consecutive days in the periovulatory period. The inseminations were timed at 14–18 h and 36–40 h post-HCG. The catheter containing washed motile fraction was inserted up to the uterine fundus and the spermatozoa were gently expelled into the uterine cavity. Subsequently the
catheter was withdrawn and the patient remained in the supine position for 30 min after the insemination (Ombelet et al., 1996).

**Sperm collection and washing procedure**

The ejaculate was always collected in a sterile plastic jar containing a buffer solution (10 ml of Earle’s balanced salt solution (EBSS, Life Science International, Paisley, UK) supplemented with penicillin, streptomycin, pyruvate and human serum albumin) in order to reduce the number of antibodies bound to spermatozoa as mentioned in previous studies (Boettcher et al., 1982; Harrison and Hennessey, 1984; Elder et al., 1990).

We used the conventional swim-up technique for normal samples (count $>20 \times 10^5$/ml, total progressive motility $>50$%). For subnormal samples we performed only one wash procedure, followed by centrifugation of the pellets on a miniPercoll gradient (1 ml 95% to 1 ml 50%). The pellets were resuspended in 1 ml EBSS + 0.3% human serum albumin. For intrauterine insemination, the samples were concentrated to 0.3 ml. For IVF, we inseminated 100,000 spermatozoa per oocyte in the absence of teratozoospermia. When <10% normal forms were found on morphological examination, oocytes were inseminated with 500,000 spermatozoa, according to the report of Oehninger et al. (1988).

**Definition of pregnancies**

Only clinical pregnancies were taken into account. Clinical pregnancies were defined by a normal gestational sac at 6 weeks of pregnancy (1984; Elder, 1988).

**Statistics**

Student’s t-test for unpaired samples was used to test the null hypothesis that no significant differences existed between female age and the mean duration of infertility in the two groups. The same

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<th>Table IIa. Overview of our 14 group I patients. Localization of antibodies (IgG and/or IgA)</th>
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H = head; M = midpiece; T = tail; H-M-T = % of sperm antibodies directed to various sites of motile spermatozoa; Oli 1 = moderate oligozoospermia (10–19 $\times 10^6$/ml); oli 2 = severe oligozoospermia (<10 $\times 10^6$/ml); Ast 1 = moderate asthenozoospermia (20–49% progressive motility); Ast 2 = severe asthenozoospermia (<20% progressive motility); Ter 1 = moderate teratozoospermia (5–9% normal forms); Ter 2 = severe teratozoospermia (<5% normal forms); Serum ASA = serum antisperm antibodies, ELISA, positive if >75 U/ml.

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<th>Table IIb. Overview of our 15 group II patients. Localization of antibodies (IgG and/or IgA)</th>
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approach was used to check for differences between IgG and IgA antibody titres in the two groups.

Results
The mean duration of infertility was 42.6 months (range 25–96) for group I and 42.1 months (range 25–120) for group II patients. There was no difference in female age between group I (mean age: 29.4 years, range 25–34) and group II (mean age: 29.6 years, range 22–35) (Table I). All patients suffered from primary infertility (no previous pregnancy). One patient in each group (group I, no. 5, group II, no. 6) suffered from mild endometriosis; no tubal block was found in any of the patients.

There was no significant difference in seminal IgG and IgA titre between the two groups, neither did the site of attachment of the sperm surface antibodies differ. Serum antibodies were positive (ELISA > 75 U/ml) in 11 patients (37.9%) and sperm agglutination was observed in five semen samples (17.2%) (Table IIa, Table IIb).

Sperm parameters were normal for sperm concentration, total count, progressive motility and morphology in 12 patients (six from each group; 41.3%). Teratozoospermia (<10% normal forms) was the most common abnormality and was found in 15 cases (51.7%, six in group I, nine in group II). Asthenozoospermia (<50% progressive motility) could only be detected in six cases (20.7%, three in both groups). Oligozoospermia (<20 x 10⁶/ml) was present in eight cases or 27.6%, equally distributed in both groups. Oligo-asthenoteratozoospermia (OAT) was observed in three patients (10.3%).

In group I, ten patients (64.3%) became pregnant after a maximum of three IUI cycles with a cycle fecundity rate of 30.3%. These included one patient who miscarried in her cycle but achieved a successful pregnancy in her second. From the remaining five, two patients conceived during the first IVF cycle while the other three patients were selected for ICSI after two or three unsuccessful IVF procedures. In two patients a very low fertilization rate (<30%) was noticed, due to poor egg quality (increased zona thickness and presence of a dark granulated ooplasm after assessment of oocyte maturity according to Veeck, 1991) (Figure 1).

In group II, seven patients (46.6%) conceived during the first treatment cycle while another seven patients became pregnant after a second or third trial. Only one patient was selected for ICSI because of a low fertilization rate during three consecutive IVF cycles (Figure 1).

In this selected population the take-home baby rate (BTH) per IUI or IVF cycle was 27.3% (9/33) and 44.4% (16/36) respectively. Conception rate per transfer was 51.5% (17/33).

The BTH was 64.3% (9/14) after three IUI cycles versus 46.6% (7/15) and 93.3% (14/15) after one and three IVF attempts respectively (Figure 1).

Discussion
It is generally accepted that male infertility may be caused by the presence of sperm surface antibodies, at least if a level of

>50% binding is reached (Bronson et al., 1984; Barratt et al., 1992).

The immunobead test (Clarke et al., 1985) and the MAR test for IgG and IgA (Jager et al., 1978; Andreou et al., 1995) are the tests of choice for sperm surface antibodies. In our study, the MAR test for IgG and IgA was used to detect male immunological infertility.

ASA are usually detectable in seminal plasma provided that a systemic response has occurred. Nevertheless, in clinical practice we observed a dichotomy between local and systemic immune response to spermatozoa and it has been reported previously that antibodies in semen should have greater clinical significance (Adeghe, 1992).

In our study population serum antibodies were positive in 11 patients or 37.9%. This is contradictory to the results of Eggert-Kruse et al. (1993) who found that all MAR positive (semen) patients were negative for circulating ASA when assessed using an ELISA technique. The meaning of this discrepancy is unclear and may be explained by the fact that serum ASA values do not sufficiently reflect the immunological situation in the semen. Serum ASA values were not helpful in predicting success in either of our groups of patients. Sperm agglutination was only infrequently observed (5/29 or 17.2%) and did not correlate with the presence of asthenozoospermia in any of our positive cases.

We also investigated the impact of immunoglobulin isotypes (IgG and IgA) and their location on the human sperm surface on fertilization in vivo and in vitro. We did not observe any
predictive value concerning success rate of immunoglobulin isotype, levels of binding or point of location on the sperm surface in this small series. Yeh et al. (1995) described the serious impact of the presence of sperm surface IgA on fertilization rates in an IVF programme, only when high levels of binding occurred. They also reported the importance of IgM as the most significant factor with regard to fertilization, especially when localized both on the head and the tail tip. The present study did not investigate IgM isotypes.

It was reported previously that the proportion of spermatozoa coated with IgG (and not IgA) antibodies became significantly reduced when washing was performed immediately after ejaculation rather than 2 h afterwards (Adeghe, 1992). IgA may indicate a poorer prognosis than IgG, probably because they inhibit sperm migration through the cervical mucus and have a greater degree of interference with fertilization (Adeghe, 1992). Since spermatozoa were always collected in a sterile jar containing buffered medium, and since our population was a predominantly IgG positive group, this may also explain the good results reported from this series. Hypothetically speaking, it seems that the use of specific sperm preparation techniques followed by insertion of the washed motile fraction up to the uterine fundus may overcome the detrimental influence of sperm antibodies upon various steps of the fertilization process.

What can be the reason for male immunological infertility, bearing in mind that, according to conventional semen analysis, the sperm quality of most of our patients had been preserved but they still had an infertility history of at least 2 years?

Inhibition of sperm transport within the female genital tract is probably the most important antifertility factor in vivo (Adeghe, 1992), suggesting that antibody-coated spermatozoa are destroyed in utero. In-vitro studies in humans have demonstrated that spermatozoal autoantibodies induce a massive leukocytosis and sperm disruption at the level of the fundus uteri and the isthmic part of the oviduct (London et al., 1985). In-vitro fertilization bypasses this adverse uterine reaction and has therefore become a very popular and effective treatment option for male infertility resulting from sperm surface antibodies (Haas, 1987; Palermo et al., 1989; Lähteenmäki, 1993; Rajah et al., 1993). Most studies report a lower fertilization rate, but once fertilization has occurred, pregnancy rates are the same or even better compared with non-immunological IVF cases (Palermo et al., 1989; Rajah et al., 1993).

Despite the fact that IVF results are very promising in male immunological cases, there is strong evidence that ovarian stimulation/IUI is a reasonable first treatment option in a substantial number of male infertility cases (Ombelet et al., 1995). A literature survey of the few papers reporting IUI in male immunological infertility cases leads to contradictory results (Francavilla et al., 1992; Lähteenmäki et al., 1995a).

Concerning economic aspects, published data indicate that the costs of IVF and embryo transfer are four to seven times the cost of a single ovarian stimulation/IUI cycle (Comhaire, 1995; Dodson, 1995; Robinson et al., 1992). In a prospective, non-randomized, cohort study followed by meta-analysis of different treatment procedures of assisted reproduction, Peterson et al. (1994) concluded that a cost-benefit analysis comparing HMG/IUI versus IVF/embryo transfer was in favour of a first line treatment with four cycles of IUI.

Our results indicate that, with the present (limited) knowledge of male immunological infertility, treatment with ovarian stimulation/IUI is a valuable first-choice method to use before starting the more invasive and expensive techniques of assisted reproduction. This study was not randomized and can be regarded as a pilot study. Therefore, we believe that a multicentric prospective randomized study is mandatory in the near future. Nevertheless, at the present stage, there appears to be no reason to perform IVF or ICSI procedures as a first line treatment in cases of male immunological infertility, even when high levels of sperm surface antibodies prevail, at least if >500 000 motile spermatozoa are recovered after washing. In future, a search to determine the clinically relevant sites of antisperm–antibody interaction will hopefully help us in directing the treatment of male immunological infertility.

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