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Analysis of medical treatment of male infertility

A.Kamischke and E.Nieschlag[1]

Institute of Reproductive Medicine of the University (WHO Collaborating Centre for Research in Human Reproduction), Münster, Germany

[1]To whom correspondence should be addressed at: Institute of Reproductive Medicine of the University, Domagkstrasses 11, D-48129 Münster, Germany: e-mail: Nieschl@uni-muenster.de

Since the first injection of a single spermatozoon into the cytoplasm of an oocyte (intracytoplasmic sperm injection, ICSI), this method has become the most successful means of treating male infertility. Even for patients long considered untreatable, a chance of paternity has become reality. Using not only ejaculated but also testicular spermatozoa, pregnancies have been achieved in the partners of patients who had never had a chance previously, including even cases with Klinefelter syndrome. However, despite the tremendous success of ICSI, most couples would prefer to conceive offspring naturally. Therefore we review the effectiveness of current conventional treatments for male infertility and analyse the chances of infertile couples to conceive spontaneously.

Key words: fertility prognosis/hypogonadotrophic hypogonadism/male infertility/meta-analysis/randomized clinical trials

Introduction

In men with infertility either no cause can be identified (idiopathic infertility) or the presumed pathology has not yet resulted in unequivocal therapies, e.g. in patients with varicoceles, leukocytes in seminal plasma, or sperm surface antibodies. Therefore, for many andrological disorders, rational treatment approaches are still lacking (Behre *et al.*, 1997).

Various uncontrolled treatments have been applied to infertile men with often questionable pathophysiological justification or merely just on an empirical basis. On the other hand, results of high quality studies are often ignored. As the problem of separating clinically relevant from irrelevant information is common to all medical disciplines, the concept of evidence-based medicine has been developed (Evidence-Based Medicine Working Group, 1992). Evidence-based andrology, however, was especially slow to be introduced compared to other clinical disciplines, notwithstanding the dramatic increase in the number of well-designed clinical trials and systematic reviews over the past decade (Olive,

1986; O'Donovan *et al.*, 1993; Vandekerckhove *et al.*, 1993; Kamischke and Nieschlag, 1998).

This review analyses the status of andrological therapies based on the best available evidence. For more detailed systematic reviews on medical treatment of male infertility, the reader is referred to the 'Subfertility module of the Cochrane database of systematic reviews' (The Cochrane Collaboration 1997, updated 1999).

Andrological diagnosis

Andrological diagnosis aims to disclose the pathology underlying infertility and to provide a reliable basis for therapeutic intervention (Nieschlag and Leifke, 1997). For male fertility diagnosis, a standardized semen analysis under internal and external quality control is mandatory (Cooper *et al.*, 1996) and should therefore be performed according to the guidelines of the World Health Organization (WHO, 1992a).

The world-wide application of the WHO recommendations for semen analysis helped to reduce the systematic bias between laboratories caused by different assessment techniques. Flow cytometry represents an objective method for counting spermatozoa, while computer-aided sperm analysis (CASA) assesses motility reliably (Yeung *et al.*, 1997). For sperm morphology, absolute values do not yet exist, but quality control could be achieved by repeated blinded assessment of the same morphology slides (Cooper, 1996). However, even if semen analysis is done with the utmost care, its predictive value remains limited. Reliable sperm function tests do not yet exist and are urgently required (ESHRE Capri Workshop, 1996).

Fertility prognosis of untreated infertile couples

The effect of any infertility treatment has to be considered with respect to the chances of a couple conceiving spontaneously. However, little is known about the magnitude of spontaneous pregnancies in untreated couples after the first year of unprotected intercourse. Most studies which address this topic either excluded partnerships with certain abnormalities (Dumphy *et al.*, 1990; Eimers *et al.*, 1994), or unspecified treatments were performed during the observation period (Collins *et al.*, 1984; Bostofte *et al.*, 1993).

The best evidence concerning the prognosis of untreated infertile couples for spontaneous pregnancies is provided by two independent cohort studies from CITES (Canadian Infertility Therapy Evaluation Study, reported by Collins *et al.*, 1995) and from Walcheren Island in the Netherlands (Snick *et al.*, 1997), which analysed unselected, well-diagnosed groups of patients (Figure 1).

The CITES study was performed at a secondary and tertiary care infertility centre. When the untreated observations of all 2198 couples enrolled were

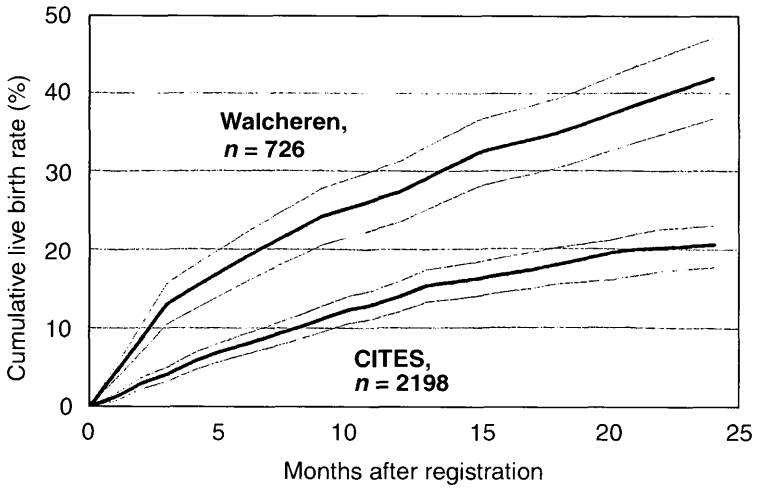

Figure 1. Cumulative live birth rates with 95% confidence intervals for infertile couples in the Walcheren Island study (n = 726) and in the Canadian Infertility Therapy Evaluation Study (CITES, n = 2198). Data were truncated after 2 years of observation for this figure (from Snick *et al.*, 1997).

considered, the cumulative rate of conceptions leading to live birth 36 months after registration for the trial was 25.2% [95% confidence intervals (CI) 21.8–28.6%]. The significantly ($P < 0.05$) relevant prognostic factors influencing pregnancy prognosis in this secondary and tertiary care subfertility population were: prior pregnancy in partnership, duration of infertility <36 months, female age <30 years, sperm defects as defined by WHO, endometriosis and tubal defects.

The Walcheren Island study was carried out at a primary care infertility centre. When the untreated observations of all 726 couples enrolled were considered, the cumulative rate of conceptions leading to live birth 36 months after registration for the trial was 52.5% (95% CI 44.7–60.2%). In a six-factor model (Table Ib) the following were identified as significantly ($P < 0.05$) relevant prognostic factors: tubal defects, ovulation defects, WHO sperm defects, secondary infertility, duration of subfertility <24 months and female age <30 years.

With the help of the identified prognostic factors, both studies arrive at prediction scores for live births in untreated infertile couples of 62% (CITES study) and 76% (Walcheren study) accuracy. When the Walcheren prediction model is applied to the data of the CITES study, the overall accuracy is 67% (95% CI 63–70%), comparable to common prediction scores in other clinical disciplines (Harrell *et al.*, 1982). However, one should admit that area under the curve (AUC) values of <50% imply an inoperative model and that therefore the overall accuracy of 67% is still suboptimal for predicting the chance of a live birth for an individual patient considered prospectively. In addition, it should be mentioned that the accuracy of fertility prediction may depend on comparable populations, as in the CITES and Walcheren studies, and therefore might be inaccurate if applied to a non-corresponding population.

In order to predict the chance of a live birth for an individual couple according

Table Ia. Average cumulative live birth prognosis of untreated infertile couples after 3, 6, 12, 24 and 36 months of expectant management according to [a]Snick *et al.* (1997) and [b]Collins *et al.* (1995)

Time to pregnancy (months)	Cumulative live birth rate (%) of infertile couples in a primary fertility centre[a]	Cumulative live birth rate (%) of infertile couples in a secondary/tertiary fertility centre[b]
3	13.0	4.2
6	18.9	8.1
12	27.4	14.3
24	41.9	21.2
36	46.2	25.2

Table Ib. Effect of prognostic factors (Walcheren model), expressed in multiplication factors (MF) of the baseline prognosis (from Snick *et al.*, 1997)

Prognostic factors identified in the Walcheren study	Effect of prognostic factors expressed in multiplication factors on the baseline prognosis
Prior pregnancy in partnership	1.5
Duration of infertility <24 months	1.5
Female age <30 years	1.4
Semen defect according to WHO	0.6
Ovulation defect	0.4
Tubal defect	0.1

to the Walcheren model, the baseline estimate of the cumulative live birth rate (Table Ia) has to be multiplied by the relative hazard for each clinical predictor (Table Ib). For example, a couple with secondary infertility [multiplication factor (MF) 1.5] of 1 year duration (MF 1.5) seeking reproductive health care for the first time, when the female partner's age is 31 years, without ovulation or tubal defects and oligozoospermia (MF 0.6) has an average 6 month cumulative live birth rate (18.9%) equivalent to 25.5% (18.9%×1.5×1.5×0.6) without treatment.

Furthermore, with the help of this prediction model, it is also possible to estimate the effect of treatment in a given couple (Collins *et al.*, 1995). For example, the effect of clomiphene citrate treatment of the woman on pregnancy was 2.2 times greater than the placebo effect (Fisch *et al.*, 1989; Deaton *et al.*, 1990; Glazener *et al.*, 1990). Thus in the above-described couple, the predicted cumulative live birth rate would be 56.1% (25.5%×2.2; individual baseline fertility prognosis×treatment effect) after 6 months of clomiphene citrate treatment (Collins *et al.*, 1995).

Criteria for analyses and meta-analysis of infertility treatments

The studies analysed were identified by computer Medline and Cochrane library searches using the keywords discussed under the following subheadings. In addition, truly randomized controlled clinical studies known to the authors were included.

Treatment options were discussed on the basis of the best trials available. Observational studies were judged adequate to demonstrate effectiveness in hormone substitution therapy of male hypogonadotrophic hypogonadism (e.g. Burgues *et al.*, 1997; Büchter *et al.*, 1998). In addition, in areas in which no controlled prospective randomized trials exist [infant therapy of maldescended testes, treatment of retrograde ejaculation, gonadotrophin-releasing hormone (GnRH) treatment in idiopathic male infertility], the evidence, albeit weak, for treatment effectiveness was also discussed in the light of observational studies.

In all other areas of medical treatment of male infertility, analysis of effectiveness of treatment was based solely on controlled clinical trials. As conception without therapy can occur in most subfertile couples over time (see above), truly randomized placebo-controlled clinical trials (e.g. Kamischke *et al.*, 1998) which had pregnancy as the outcome measurement were regarded as providing the best evidence for treatment efficacy, followed by pseudorandomized controlled clinical trials (e.g. Schill, 1978). Cross-over studies were only included in this analysis if pregnancy rates could be calculated separately from the overall outcome for the first (randomized controlled) treatment phase (e.g. Bals-Pratsch *et al.*, 1992). More details of the studies included in the analysis are discussed under the subheading of each investigated drug.

Because pregnancies among infertile couples occur relatively infrequently, the number of patients that has to be included in a trial on the basis of a power estimate is usually larger than the number available. In addition, results of several studies have been contradictory or inconclusive and even if results of single high quality studies are consistently non-significant, an overall significant effect might be overlooked. To overcome this problem, data were considered for meta-analysis from patients in whom the same or similar drugs were evaluated in several smaller but comparable trials, and these data also contributed to considerations about the generalization of the study results (Egger and Smith, 1997).

Studies were judged suitable for pooling and meta-analysis in areas where more than one randomized controlled clinical trial with the relevant outcome parameter 'pregnancy' could be identified. Before studies were pooled for meta-analysis, identified trials were tested for homogeneity using the χ^2 test and graphical approaches, with the assumption that if confidence intervals for the results of the included studies overlapped, differences between single studies could be considered statistically insignificant and therefore the studies homogeneous (Egger *et al.*, 1997). All homogeneous trials were subjected to meta-analysis using the RevMan software (The Cochrane Collaboration, 1997) and applying the fixed model Peto-modified Mantel–Haenszel technique (Yusuf *et al.*, 1985). The results of each trial and of the combined evaluation of all homogeneous trials for the dichotomous outcome pregnancy were given as an odds ratio with 95% CI. Odds ratios greater than one (risk differences greater than zero) always indicated that treatment was better. Where the 95% CI was entirely above or below 1, the treatment group did significantly (at 5% level) better or worse than the control group.

Conventional male infertility treatment

Secondary hypogonadism/gonadotrophin deficiency

In male hypogonadal patients with hypothalamic or pituitary dysfunction, GnRH and/or gonadotrophin treatment has been applied successfully for many years. Outcome and adjustment parameters for therapy are serum testosterone concentrations, testicular growth, appearance of spermatozoa in the ejaculate and induction of pregnancy.

The dose of human chorionic gonadotrophin (HCG) should be adjusted to the testosterone and oestradiol serum concentrations, which should not exceed normal values. Doses commonly used are 1000–2500 IU HCG twice a week combined with human menopausal gonadotrophin (HMG) 150 IU three times weekly (Burgues *et al.*, 1997; Büchter *et al.*, 1998). GnRH therapy consists of 5–20 μg GnRH every 120 min and should be adjusted to reproductive hormone concentrations (Büchter *et al.*, 1998). Treatment efficacy for both therapies is similar, although GnRH treatment has a tendency for higher success in some studies (Schopohl *et al.*, 1991; Schopohl, 1993). Induction of spermatogenesis and paternity can be expected in 80–88% within 1 year in most cases (Burgues *et al.*, 1997; Büchter *et al.*, 1998). It is important to note that patients usually become fertile with sperm concentrations far below the normal limit (Büchter *et al.*, 1998; Burris *et al.*, 1988). In consecutive courses of treatment, time to induction of spermatogenesis is shorter than in the first stimulation cycle. Therefore, it is advisable to induce spermatogenesis even before paternity is desired, to assure the patient that paternity is possible and to reduce time to pregnancy when it is desired (Kliesch *et al.*, 1995).

Whether recombinant gonadotrophins (Kliesch *et al.*, 1995) are superior to HCG/HMG for achieving paternity in patients with hypogonadotrophic hypogonadism has not been demonstrated to date, but would be the appropriate subject for prospective, randomized controlled trials.

Retrograde ejaculation

Retrograde ejaculation is mainly caused by injury to the lumbar sympathetic nerves (e.g. retroperitoneal lymphadenectomy) or by surgery that damages the neck of the bladder. Diagnosis is confirmed when a substantial number of spermatozoa can be detected in the urine after ejaculation. For reversal of retrograde ejaculation, α-adrenergic agonists (phenylpropanaline 25 mg per os twice daily, oxedrine 15–60 mg i.v.), anticholinergics (brompheniramine maleate 8 mg per os twice daily), and imipramine (25–50 mg per os daily), which facilitate ejaculation by stimulating peristalsis in the vas deferens and closing the neck of the bladder, have all been used (Herschlag *et al.*, 1991). However, to our knowledge, not a single controlled study concerning the medical treatment of retrograde ejaculation has been reported. Evidence concerning efficacy mostly comes from small cohort studies ($n < 20$) or case reports. These observational

studies suggest an efficacy for antegrade ejaculation in 28–83% of patients treated (Jonas *et al.*, 1979; Nijman *et al.*, 1982; Goldwasser *et al.*, 1983; Eppel and Berzin, 1984; Drawz and Drawz, 1992), with a consecutive pregnancy rate of 40–50% (Nijman *et al.*, 1982; Drawz and Drawz, 1992). In addition, treatment efficacy might be better if the drugs are given for several days before the semen specimen is collected. Because of the weak evidence for efficacy of medical treatment of retrograde ejaculation, truly randomized trials are needed. If medical reversal of retrograde ejaculation fails, spermatozoa can be recovered by electrovibration or surgery.

Testicular maldescent

In the past 30–40 years maldescended testes were estimated to occur in 3–6% of males at birth, but there are few reliable studies with sufficient population numbers (Hutson *et al.*, 1997). As germ cell degeneration and dysplasia start in early infancy, the position of the maldescended testes should be corrected by the end of the first year of life or earlier because of the 5- to 10-fold higher risk for testicular tumours (Huff *et al.*, 1993). Therapy of maldescended testes in childhood by GnRH or HCG has only been successful in 10–20% of individuals in randomized clinical trials (de Muinck Keizer-Schrama *et al.*, 1986; Raifer *et al.*, 1986; Hoorweg-Nijman *et al.*, 1994), and therefore if endocrine therapy fails, orchidopexy should be performed (Deutsche Gesellschaft für Endokrinologie, 1991).

Because of earlier treatment, few cases present in the infertility clinic with testes that are still in an abnormal position (Nieschlag, 1997). However, most studies investigating the influence of formerly maldescended testes on infertility had no appropriate control group or were too small in size to allow for statistical comparison of time to conception. In a recent large observational cohort study comparing a control population with a population of previously bilaterally or unilaterally maldescended testes (mean age at orchidopexy 7 years), only the patients with previously bilaterally maldescended testes were afflicted by infertility, as their time to pregnancy was considerably longer compared to controls and to patients with previously unilaterally maldescended testes (Coughlin *et al.*, 1997). As no significant differences could be detected between men with previously unilaterally maldescended testes and controls, it is possible that the contralateral descended testis may compensate for damage to the formerly maldescended testis and functions as a prime contributor of spermatozoa (Coughlin *et al.*, 1997).

Whether earlier treatment of testicular maldescent as practised today prevents infertility and testicular cancer compared to later treatment has not yet been resolved, as the patients treated earlier in life are only now beginning their reproductive phase (Nieschlag, 1993). Apart from preventive therapy, maldescent-related infertility has the same treatment options as idiopathic infertility.

Varicocele

Varicoceles are believed to cause testicular and epididymal damage via hypoxia and stasis, increased testicular pressure, elevated spermatic vein catecholamines and increased testicular temperature (Zorgniotti and McLeod, 1973; Comhaire and Vermeulen, 1974; Netto *et al.*, 1977; Gorenstein *et al.*, 1986) and are the most frequent physical finding in infertile men (WHO, 1992c; Behre *et al.*, 1997). Ligation, embolization or sclerosing of the spermatic vein have long been accepted as the treatment of choice (Takihara *et al.*, 1991) and varicocelectomy has become the most common operation for male infertility (McClure and Hricak, 1986).

However, despite the common practice for decades of performing varicocelectomy, the evidence of treatment efficacy was based on non-randomized uncontrolled trials (Marsman and Schats, 1994). Only a few and mainly recent randomized controlled clinical trials with relevant outcome parameters (improvement in sperm parameters, induction of pregnancy) have been published (Nilsson *et al.*, 1979; Breznik *et al.*, 1993; Madgar *et al.*, 1995; Nieschlag *et al.*, 1995, 1998; Yamamoto *et al.*, 1996; Hargreave, 1997).

Two trials which were originally planned as one WHO multicentre trial (Madgar *et al.*, 1995; Hargreave, 1997) suggested significant benefits for male fertility after surgical varicocele repair (pregnancy rates 60 and 34.8%) compared with unoperated controls (pregnancy rates 10 and 16.7%). However, in both studies the control groups remained completely untreated, not even counselled, ignoring the existence of unspecific (placebo) effects associated with any medical intervention.

The other four randomized clinical trials showed no significant effect of varicocelectomy on pregnancy rates compared to controls (Nilsson *et al.*, 1979: 7.8 versus 17.8%; Breznik *et al.*, 1993: 34.2 versus 53.7%; Nieschlag *et al.*, 1998: 25.5 versus 27.1%; Yamamoto *et al.*, 1996: 6.7 versus 10%). However, as in the two previous trials, difficulties could be detected in three out of the four studies (Nilsson *et al.*, 1979; Breznik *et al.*, 1993; Yamamoto *et al.*, 1996) despite the controlled design. The study by Nilsson *et al.* (1979) showed a pregnancy rate of only 12% despite an observation period of 5 years, casting doubt on the integrity of female reproductive functions. Moreover, in the study by Breznik *et al.* (1993), female factors might have been overlooked, as normozoospermia was diagnosed in 30% of patients involved in the trial. The low pregnancy rates in the study by Yamamoto *et al.* (1996) may be explained by the fact that only subclinical varicoceles were investigated and their significance remains questionable.

For reasons of heterogeneity, the studies of Magdar *et al.* (1995) and Hargreave (1997) had to be excluded before meta-analysis of the remaining four randomized clinical trials on the effect of varicocele treatment on pregnancy rate (from Nieschlag *et al.*, 1998: only the update was included). However, individual odds ratios of both excluded studies were also presented, together with the results of the studies included in the analysis and their combined odds ratio (Figure 2).

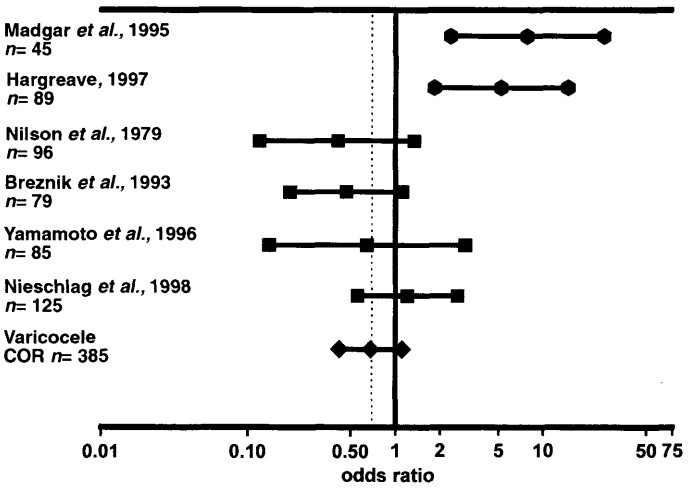

Figure 2. Individual or combined odds ratios (COR) of induced pregnancies based on analysis of randomized, controlled clinical trials on varicocele treatment. Results are presented as odds ratio with 95% confidence intervals. The dashed line represents the COR of all included studies (squares) indicating homogeneity. In addition, the two randomized controlled trials not included in the meta-analysis are shown (circles).

Meta-analysis of the results from the 385 patients involved in the analysis revealed no significant difference in the cumulative pregnancy rate (odds ratio 0.69; 95% CI 0.42–1.13) and emphasizes the importance of properly designed control groups and significance of bias. In view of the clinically invasive intervention, this option becomes clinically irrelevant. Since it remains questionable whether interventive treatment is superior to no treatment or to counselling in terms of fertility, intervention cannot currently be recommended.

Infections

Major acute symptomatic bacterial infections or venereal diseases of the genital tract should be treated with antibiotics in order to prevent occlusions of the efferent ducts. Also, viral orchitis is known to lead to possible profound impairment of spermatogenesis and infertility, but can be treated only symptomatically in the acute phase or preventively by vaccination in the case of mumps.

However, the aetiology and biological significance of white blood cells in semen and asymptomatic subclinical genital tract infections with *Chlamydia* or other micro-organisms, as well as the role of antibiotic treatment in these cases, remain unclear (Wolf, 1995; Eggert-Kruse *et al.*, 1997). Only a very limited number of randomized controlled studies dealing with asymptomatic genital tract infections have been performed so far, and they either aim to resolve the rate of leukocytospermia (Branigan and Muller, 1994; Yanushpolsky *et al.*, 1995) or to eliminate bacteria (Harrison *et al.*, 1975; Hinton *et al.*, 1979; Comhaire *et al.*, 1986).

The incidence of leukocytospermia showed a high spontaneous resolution rate in treatment and control groups after 1 month of observation (Branigan and

Muller, 1994; Yanushpolsky *et al.*, 1995), but if the patients were examined for a longer follow-up period (Branigan and Muller, 1994), a persistent resolution rate of leukocytospermia was only apparent in the treatment group with frequent ejaculation and antibiotic treatment. No differences were seen in semen parameters between treatment and control groups in these randomized controlled clinical trials. When pregnancies were evaluated (Branigan and Muller, 1994), the highest pregnancy rate was observed in the frequent-ejaculation plus doxycycline group (14.8%), followed by the frequent-ejaculation alone and the doxycycline alone groups (each 8%) and the no-treatment group (4%).

Antibiotic treatment in two (randomized, placebo-controlled trial: Harrison *et al.*, 1975; randomized, placebo-controlled, cross-over trial: Hinton *et al.*, 1979) out of three studies led to a higher resolution of bacterial infection (*Mycoplasma hominis*, *Ureaplasma urealyticum*) compared to untreated or placebo patients. However, not all patients involved in these studies were infected. In contrast to these trials, another randomized placebo-controlled trial (Comhaire *et al.*, 1986) did not detect any differences in bacterial resolution rate. Pregnancy rates in all three studies were not different compared to the control group, neither did sperm parameters differ where evaluated (Comhaire *et al.*, 1986).

For meta-analysis, the study treating leukocytospermia and having pregnancy as an outcome parameter (Branigan and Muller, 1994) was combined with the available randomized trials treating bacterial infection and having pregnancy as an outcome parameter (Harrison *et al.*, 1975; Hinton *et al.*, 1979; Comhaire *et al.*, 1986). For the data from the 187 patients in these trials, meta-analysis revealed no significant influence (odds ratio 1.76; 95% CI 0.70–4.46) of antibiotic treatment on pregnancy rates in asymptomatic genital tract infections. Number-needed-to-treat (NNT) analysis of all the studies together revealed that 19 patients have to be treated to achieve one pregnancy more than in the untreated population. In view of the possible side-effects, antibiotic treatment of asymptomatic genital tract infections cannot be recommended.

Immunological male infertility

The term 'immunological male infertility' mainly refers to the detection of antisperm antibodies in the seminal fluid of men whose infertility is otherwise unexplained. The clinical significance of different concentrations of antisperm antibodies is yet not well established. In addition, associations of antisperm antibodies with leukocytospermia and subclinical infection (Paschke *et al.*, 1994a; Ekwere, 1995; Mahmoud *et al.*, 1996) or other autoantibodies (Paschke *et al.*, 1994b) have been described and further complicate the concept of immunological infertility.

Findings of three prospective, controlled studies based mainly on laboratory tests supported the relevance for male fertility of immunoglobulin (Ig)G- and in particular IgA-class antisperm antibodies yielding a positive mixed agglutination reaction (MAR) test >30% on the sperm surface (Eggert-Kruse *et al.*, 1991,

1995; Mahmoud *et al.*, 1996), while another prospective controlled study showed no effects of antisperm antibodies on fertility (Collins *et al.*, 1993). Abshagen *et al.* (1998) showed that antisperm IgG or IgA antibodies above a concentration of 50% led to significantly reduced pregnancy rates and a concentration >90% almost excluded the chance for a spontaneous pregnancy.

Drugs having an immunosuppressive effect, such as glucocorticoids, have been used in an attempt to reduce antisperm antibody concentrations. Randomized, placebo-controlled studies focusing on sperm parameters have shown no effect of such therapy on serum antisperm antibody concentrations or semen characteristics compared to placebo (De Almeida *et al.*, 1985). In contrast, a marked decrease in the proportion of spermatozoa positive for IgG and IgA antibodies (Rasanen *et al.*, 1996) has also been described.

As no truly randomized trials were available, four randomized (Haas and Manganiello, 1987; Hendry *et al.*, 1990; Bals-Pratsch *et al.*, 1992; Lahteenmaki *et al.*, 1995) placebo-controlled studies (two cross-over studies) and two (Gregoriou *et al.*, 1996; Omu *et al.*, 1996) randomized controlled studies (one cross-over study) having spontaneous ($n = 4$) and assisted reproduction pregnancies ($n = 2$) as outcome parameter were analysed. Two studies (Hendry *et al.*, 1990; Omu *et al.*, 1996) claimed a beneficial effect of corticosteroid therapy on the conception rate, while the other authors concluded no beneficial effect of corticosteroid therapy.

Despite some clinical differences in patient diagnosis and study design, four studies were grouped together for pregnancy analysis in a meta-analysis on corticosteroid treatment (Haas and Manganiello, 1987; Bals-Pratsch *et al.*, 1992; Lahteenmaki *et al.*, 1995; Omu *et al.*, 1996). Two cross-over studies (Hendry *et al.*, 1990; Gregoriou *et al.*, 1996) had to be excluded as single pregnancy analysis was not possible for the first treatment phase before crossing over. Meta-analysis revealed no significant influence (odds ratio 2.02; 95% CI 0.88–4.61) of corticosteroid treatment on pregnancy rates in 190 patients presenting with immunological infertility (Figure 3).

However, despite an overall odds ratio bordering the 5% significance level, conclusions from this meta-analysis have to be drawn with caution, as the number of patients analysed in qualitatively adequate studies and the power in this meta-analysis are both still low. In addition, the potential benefit of corticosteroids has to be seen in perspective, taking into consideration the possibly severe side-effects of corticosteroid treatment, such as muscle and bone loss, including aseptic necrosis of the femoral heads, generalized infections, gastric disorders and weight gain. To clarify the potential benefits together with the potential side-effects of corticosteroid treatment, well-designed clinical studies should reassess this issue before drawing further conclusions. For the time being, patients with high concentrations of antisperm antibodies seem to benefit from ICSI treatment.

Idiopathic male infertility

Despite the uncertain diagnosis of 'idiopathic infertility', which probably has many different underlying pathophysiological causes, in the past many empirical

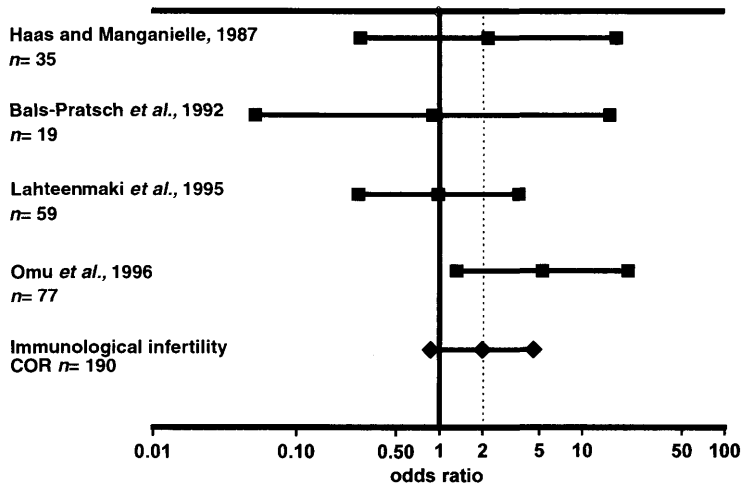

Figure 3. Individual (squares) or combined odds ratios (COR; diamonds) of induced pregnancies based on analysis of randomized, controlled clinical trials on immunological infertility treatment. The dashed line represents the COR of all included studies indicating homogeneity. Results are presented as odds ratio with 95% confidence intervals.

therapies have been applied (O'Donovan *et al.*, 1993; Vandekerckhove *et al.*, 1993; Kamischke and Nieschlag, 1998).

Hormonal treatment

GnRH treatment

Since GnRH, gonadotrophins and testosterone are effective in the treatment of hypogonadism, their application was tried in idiopathic male infertility under the assumption that elevated follicle stimulating hormone (FSH) might be caused by disturbances of GnRH pulses in patients with oligoasthenoteratozoospermia. However, only uncontrolled trials are available, in part showing opposing results, so that no conclusions for treatment efficacy can be drawn.

HCG/HMG

Treatment of idiopathic male infertility with HCG/HMG was used for many years, and many uncontrolled studies have been published, with a review of 39 uncontrolled studies reporting pregnancy rates of 8–14% on average (Schill, 1986).

In contrast to these studies, the only available randomized, double-blind, placebo-controlled, cross-over study of HCG/HMG treatment for normogonadotrophic oligoasthenoteratozoospermic men did not demonstrate any beneficial effect on sperm parameters or pregnancy rates (Knuth *et al.*, 1987), suggesting the inefficacy of the approach.

Purified HMG preparations and recombinant FSH

Promising results in monkeys (van Alphen *et al.*, 1988; Weinbauer *et al.*, 1992) and in an uncontrolled study (Acosta *et al.*, 1992) have led to a reconsideration

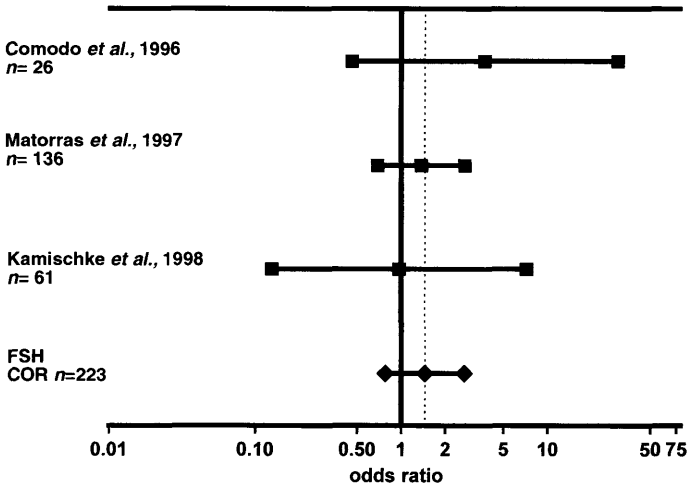

Figure 4. Individual (squares) or combined odds ratios (COR; diamonds) of induced pregnancies based on analysis of randomized, controlled clinical trials with pure follicle stimulating hormone (FSH) or recombinant FSH treatment. The dashed line represents the COR of all included studies indicating homogeneity. Results are presented as odds ratio with 95% confidence intervals.

of FSH treatment in male infertility, but the need for double-blind, placebo-controlled studies has been stressed (Baker *et al.*, 1992; Simoni and Nieschlag, 1995). So far, three randomized controlled clinical trials with highly purified HMG or recombinant FSH have been published as peer-reviewed papers (Matorras *et al.*, 1997; Kamischke *et al.*, 1998) or as abstracts (Comodo *et al.*, 1996). None of these randomized, placebo-controlled (Comodo *et al.*, 1996; Kamischke *et al.*, 1998) or randomized controlled trials (Matorras *et al.*, 1997) showed any improvement of conventional semen parameters compared to placebo or baseline values, although one study (Kamischke *et al.*, 1998) showed increased testicular volume and higher sperm DNA condensation in the verum group. In contrast to the majority of uncontrolled studies, none of the controlled studies detected a significant increase in pregnancy rates due to FSH treatment. Meta-analysis of all randomized studies showed no significant influence (odds ratio 1.45; 95% CI 0.78–2.70) of purified or recombinant FSH treatment on pregnancy rates in 223 patients (Figure 4). NNT analysis of all the studies together revealed that 22 patients have to be treated to achieve one pregnancy more than in the untreated population. In view of the high costs of FSH therapy and the questionable benefits, FSH treatment, as practised today, cannot be recommended.

Androgens

Administration of supplementary exogenous testosterone (especially mesterolone) has been proposed as a therapy for idiopathic infertility for over two decades on the basis of uncontrolled studies, despite the fact that androgens have been shown to be effective in suppressing spermatogenesis, even to the extent of causing azoospermia, in various trials of male contraception. Of 13 randomized trials performed, nine randomized placebo-controlled, double-blind studies (Mauss,

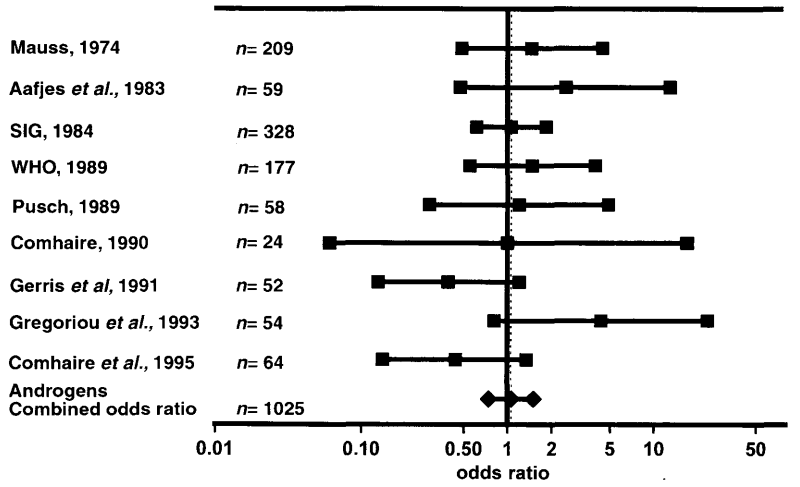

Figure 5. Individual (squares) or combined odds ratios (COR; diamonds) of induced pregnancies based on analysis of randomized, controlled clinical trials with androgen treatment. The dashed line represents the COR of all included studies indicating homogeneity. Results are presented as odds ratio with 95% confidence intervals.

1974; Aafjes *et al.*, 1983; Scottish Infertility Group, 1984; Pusch, 1989; WHO, 1989; Comhaire, 1990, Gerris *et al.*, 1991, Gregoriou *et al.*, 1993; Comhaire *et al.*, 1995) with androgens and pregnancy as outcome parameter could be identified. In one trial (Scottish Infertility Group, 1984), the placebo given to the control group was vitamin C. Although vitamin C has been claimed by some to be an effective treatment for male infertility (Dawson *et al.*, 1992), the dose employed in this trial (200 mg daily) was much lower than that used in clinical trials. At the dose used, the effect of the vitamin C in this trial was considered to have no specific effect on the outcome parameters and was reasonably considered as a placebo by the authors. Despite the fact that five studies proposed a beneficial effect of treatment, none of the individual trials showed a significant effect on pregnancy rates. Meta-analysis of randomized, placebo-controlled trials revealed no significant influence (odds ratio 1.02; 95% CI 0.72–1.44) of androgens on pregnancy rates in 1025 patients (Figure 5). NNT analysis of all studies together revealed that 359 patients have to be treated to achieve one pregnancy more than in the untreated population! Since there is no evidence and no rationale for effectiveness from controlled studies, use of androgens would be a poor choice for therapy (O'Donovan *et al.*, 1993; Kamischke *et al.*, 1998; Vandekerckhove *et al.*, 1998a).

Anti-oestrogens

Anti-oestrogenic compounds competitively blocking oestrogens at the receptor site might reduce inhibitory feedback and lead to elevation of gonadotrophin and testosterone serum concentrations. Of 11 randomized trials performed, five truly randomized, placebo-controlled studies (Ronnberg, 1980; Scottish Infertility Group, 1982; Török, 1985; Sokol *et al.*, 1988; WHO, 1992b) and one randomized,

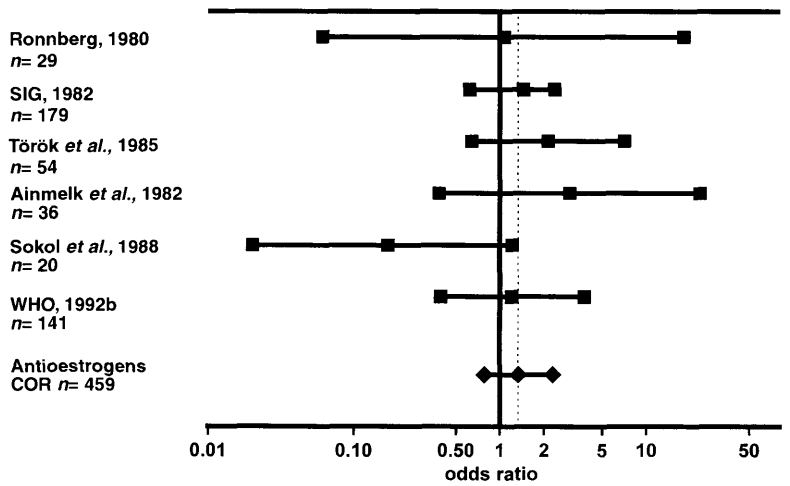

Figure 6. Individual (squares) or combined odds ratios (COR; diamonds) of induced pregnancies based on analysis of randomized, controlled clinical trials with anti-oestrogen treatment. The dashed line represents the COR of all included studies indicating homogeneity. Results are presented as odds ratio with 95% confidence intervals.

double-blinded study with an unstated (Ainmelk *et al.*, 1982) method of randomization were identified. In one trial (Scottish Infertility Group, 1982), the placebo given to the control group was vitamin C (see comments in the Androgen subsection above). Neither treatment with tamoxifen nor clomiphene showed any significant therapeutic effect on pregnancy rates in a single study. Meta-analysis of all the above-mentioned randomized, placebo-controlled trials showed no significant influence (odds ratio 1.33; 95% CI 0.78–2.28) of anti-oestrogens on pregnancy rates in 459 patients analysed (Figure 6). NNT analysis of all studies together revealed that 29 patients have to be treated to achieve one pregnancy more than in the untreated population. If studies that were not truly randomized or not placebo-controlled are included in the analysis, only a small beneficial effect of anti-oestrogens remains plausible (Vandekerckhove *et al.*, 1998b), which has to be counterbalanced by their potentially toxic side-effects (for review, see Rolf *et al.*, 1996).

Non-hormonal therapies

Although the role of the kinin system in spermatogenesis is not clearly defined, kallikrein has been widely used for the treatment of idiopathic male infertility in andrological practice in continental Europe and Japan. Sixteen randomized trials [kallikrein or angiotensin-converting enzyme (ACE) inhibitors] with pregnancy as an outcome parameter have been performed with this drug, but only three were truly randomized (Bedford and Elstein, 1981; Glezerman *et al.*, 1993; Keck *et al.*, 1994) and two additional trials were double-blinded with the method of randomization not stated (Izzo *et al.*, 1984; Schill *et al.*, 1994). Taken alone, none of these studies showed a significant effect of kallikrein or ACE inhibitors on sperm parameters or pregnancy rates. Of the other randomized trials, one

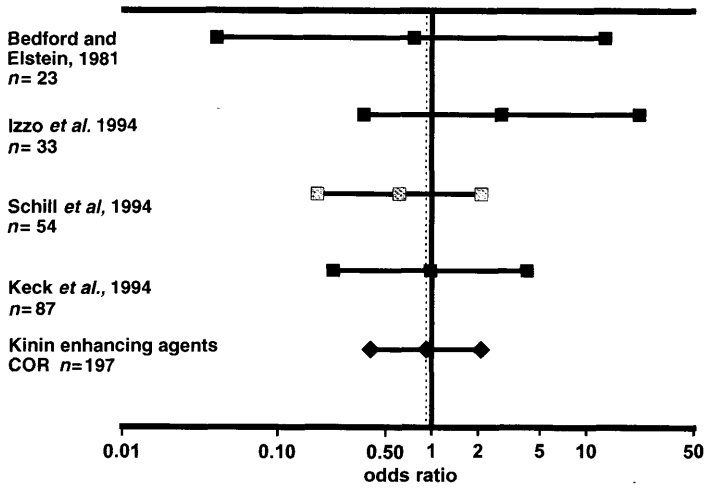

Figure 7. Individual (squares) or combined odds ratios (COR; diamonds) of induced pregnancies based on analysis of randomized, controlled clinical trials of treatment with kinin-enhancing agents (kallikrein: open symbols; ACE-inhibitors: closed symbols). The dashed line represents the COR of all included studies indicating homogeneity. Results are presented as odds ratio with 95% confidence intervals.

pseudo-randomized (Schill, 1978) and one not placebo-controlled (Micic *et al.*, 1985) did, however, demonstrate a significant positive effect of kallikrein on pregnancy rates. The randomized, double-blinded, placebo-controlled trials having pregnancy as an outcome were analysed together (Bedford and Elstein, 1981; Izzo *et al.*, 1984; Keck *et al.*, 1994; Schill *et al.*, 1994), which revealed no significant influence (odds ratio 0.92; 95% CI 0.40–2.08) of kinin-enhancing agents on pregnancy rates in nearly 200 patients (Figure 7). In view of the results of these high-quality studies, and as a less restrictive analysis of non-truly randomized studies showed beneficial effects due only to absent pregnancies in the control groups, kinin-enhancing agents should only be used in the context of clinical trials (Vandekerckhove *et al.*, 1998c).

Bromocriptine has been applied previously for idiopathic male infertility because it is effective in treating hyperprolactinaemia, and on the assumption that prolactin may play a direct role in spermatogenesis and reproductive hormone production. Three randomized placebo-controlled and double-blinded trials were identified (Hovatta *et al.*, 1979; Glatthaar *et al.*, 1980; Ainmelk *et al.*, 1982). No beneficial effects on the verum group were reported in terms of sperm parameters or pregnancy rates, suggesting that bromocriptine treatment promises no benefit.

Other non-hormonal therapies for idiopathic male infertility include the antioxidants vitamin C (Dawson *et al.*, 1992) and vitamin E (Kessopoulou *et al.*, 1995; Moilanen and Hovatta, 1995; Suleiman *et al.*, 1996) and gluthathione (Lenzi *et al.*, 1993). Despite an existing pathophysiological concept for the antioxidants, most published studies were not truly randomized, or randomization was not stated, or the medication was not applied to infertile patients (Dawson *et al.*, 1992). No significant improvements in semen characteristics of infertile patients were reported by one study (Moilanen and Hovatta, 1995), while the

others found improvements in sperm function due to the antioxidants (Lenzi *et al.*, 1993; Kessopoulou *et al.*, 1995; Suleiman *et al.*, 1996). One study showed a marked effect of vitamin E treatment on pregnancy rates (Suleiman *et al.*, 1996), while the other study showed no effect (Kessopoulou *et al.*, 1995). Meta-analysis of these two trials showed a significant effect of vitamin E on pregnancy rates (odds ratio 4.03; 95% CI 1.36–11.96), although the meta-analysis was markedly biased by the study showing a significant effect on pregnancy rates on its own (Suleiman *et al.*, 1996), which was mainly due to the missing pregnancies in the placebo group despite a 6-month follow-up. Further evidence concerning the efficacy of vitamin E in infertile men should be evaluated in good-quality trials before it can be recommended.

Conclusions

Apart from rational treatment of secondary hypogonadism, with its underlying clear pathophysiological concept, ineffective medical treatments of male infertility (androgens, anti-oestrogens, kinin-enhancing agents, purified HMG, treatment of varicocele) have been used for decades. As proof of their ineffectiveness was provided only late after their introduction, the importance of high quality studies early on is emphasized. Considering that most couples wish to conceive offspring naturally, new therapeutic regimes based on solid pathophysiological findings and more sophisticated diagnostic tools are required. In addition, controlled studies appear warranted in areas where the current evidence of effectiveness is weak (e.g. treatment of retrograde ejaculation) or only a few controlled studies have been performed (e.g. treatment of subclinical infection and immunological infertility, vitamin E treatment). It appears important to estimate accurately the baseline prognosis of an untreated couple for pregnancy. Only couples with a poor prognosis for spontaneous pregnancy should be submitted to symptomatic therapy (i.e. ICSI).

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