Article

IUI in male subfertility: are we able to select the proper patients?

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Abstract

There is at this time no indication as to which semen parameters from the fertility work-up discriminate between couples with male subfertility who will and will not benefit from intrauterine insemination (IUI). This study evaluated the predictive capacity of semen parameters (both pre- and post-wash) and antisperm antibodies (ASA) obtained during the fertility work-up on IUI outcome in couples with male subfertility in a retrospective cohort study. It included 290 couples, who underwent 722 IUI cycles. The overall ongoing pregnancy rate was 9% per cycle. Model I, with female age, duration of subfertility, secondary subfertility, the presence of anovulation, cervical hostility and cycle number had an area under the curve (AUC) of 0.59. Adding the presence of ASA to this model improved the AUC to 0.65 (model II). Further addition of the post-wash total motile count (TMC) to the model with ASA (model III) improved the AUC to 0.67. Using the models to exclude couples from IUI due to low expected pregnancy rates would increase the pregnancy rate to 11% per cycle with model I, and to 14% per cycle for model II and for model III. In conclusion, in the selection of patients with male subfertility for IUI, the use of prediction models including ASA can increase the efficiency of IUI.

Keywords: *intrauterine insemination, male subfertility, pregnancy and semen parameters, prognostic factors*

Introduction

Decision making and patient counselling in reproductive medicine for intrauterine insemination (IUI), IVF or intracytoplasmic sperm injection (ICSI) in male subfertility is often difficult. The various semen parameters that are combined in the standard semen analysis (i.e. sperm count, motility, morphology, total motile count) and the semen parameters after processing have been extensively investigated regarding their relationship with IUI outcome (Francavilla *et al.*, 1990; Campana *et al.*, 1996; Milingos *et al.*, 1996; Tomlinson *et al.*, 1996; Branigan *et al.*, 1999; Dickey *et al.*, 1999; Montanaro *et al.*, 2001; Van Voorhis *et al.*, 2001; Lee *et al.*, 2002; Miller *et al.*, 2002; Ombelet *et al.*, 2003; van Weert *et al.*, 2004). Most studies, however, report on semen parameters at the time of the actual insemination, which obviously eliminates these semen parameters as a tool for counselling before the start of treatment. The studies that report on the semen parameters during fertility work-up lack a multivariate approach that takes into account all variables known to influence IUI outcome. This limits their use in daily clinical practice.

At present, there are no studies on IUI in male subfertility that provide data to aid the clinician in identifying those couples who will benefit from IUI and couples who will not. The present study was therefore initiated to evaluate the prognostic and clinical value of all parameters obtained during the fertility work-up in a cohort study among consecutive couples undergoing IUI for male factor subfertility. The study has specifically investigated the additional value of presence of antisperm antibodies (ASA) and the post-wash total motile count (post-wash TMC) on baseline characteristics of the couple.

Materials and methods

Patients

The study included data from all couples diagnosed with male subfertility that underwent IUI between January 1997 and December 2004 in the Academic Medical Centre, Amsterdam, The Netherlands. Male subfertility was defined as more than one semen analysis that did not meet the WHO criteria for concentration, motility and/or morphology (i.e. concentration of ≤20 × 10^6/ml, progressive motility of ≤50%, and ≤30% spermatozoa with normal morphology) (World Health Organization, 1992). Couples undergoing IUI with heterologous semen were excluded from the study.

All couples had been trying to conceive for at least 12 months. Ovulation was assessed using a basal body temperature curve, mid-luteal progesterone concentration and/or transvaginal sonography. Tubal patency was assessed by hysterosalpingography and/or laparoscopy. Couples were considered to be candidates for treatment with IUI if the woman was ovulatory, with or without ovulation induction, and if she had at least one patent tube, either at hysterosalpingography or at laparoscopy.

All male patients had at least two semen analyses during the fertility work-up. Similar to other authors, the mean for sperm concentration, motility and morphology of all the semen analyses per patient was used for statistical evaluation (Tielemans *et al.*, 1997; Goverde *et al.*, 2000; Van Voorhis *et al.*, 2001). In all patients, a post-wash TMC was performed during the fertility work-up. Until 2001, it was standard procedure not to perform IUI when there were less than 1 × 10^6 motile spermatozoa in the ejaculate after preparation. In 2001, the cut-off value was changed to more than 3 × 10^6 motile spermatozoa for eligibility for IUI (Repping *et al.*, 2002).

General patient information collected included patient's age, subfertility being either primary or secondary, subfertility diagnosis, duration of subfertility, ovulatory status and semen parameters. Cycle-specific information that could be obtained before the start of an IUI cycle included the use of ovarian stimulation, the type of stimulation and cycle number.

An ongoing pregnancy, defined as positive fetal cardiac activity of at least one fetus at 12 weeks gestation, was considered as the primary outcome of this study.

IUI protocol

Intrauterine insemination was performed in spontaneous cycles as well as in stimulated cycles. From January 1997 to December 1998, patients underwent ovarian stimulation using clomiphene citrate as the standard protocol. From January 1999, ovarian stimulation was performed with recombinant-FSH, follitropin (Puregon®; Organon, Oss, The Netherlands or Gonal-F®; Serono Benelux BV, the Hague, The Netherlands). Follicle growth was monitored by transvaginal sonography in all patients during the IUI cycle. In cases of IUI in a spontaneous cycle, the endogenous LH surge was detected by a urinary semi-quantitative monoclonal antibody kit (OvuQuick; Quid San Diego, CA, USA). Semen was inseminated 20–30 h after this detection. Human chorionic gonadotrophin (Pregnyl; Organon) was administered in a single dose of 10,000 IU when one follicle had at least a diameter of 18 mm and no LH surge was detected in the urine. Semen was inseminated 40 h later. A total of 0.3 ml suspension of processed spermatozoa was introduced into the uterine cavity with a catheter (International Medical, Zutphen, The Netherlands). The cycle was cancelled if more than three follicles of ≥16 mm were present.

Semen analysis and processing

Semen analysis was performed according to WHO guidelines (World Health Organization, 1992). Anti-sperm antibodies on the surface of the spermatozoa in the ejaculate were detected by the mixed agglutination reaction (MAR), with a cut-off for a positive test result, i.e. positive ASA, of 10% of spermatozoa with anti-sperm antibodies on the surface (World Health Organization, 1992).

Patients had minimal sexual abstinence of 2 days and analysis of the semen was performed within 1 h of ejaculation. Data on the maximum sexual abstinence period were not obtained, since that was not a routine question in the semen analysis protocol. After liquefaction, volume, concentration and motility were determined. Semen was diluted 1:1 with culture medium (Ham's-F10; Invitrogen, Breda, The Netherlands) or human tubal fluid (Cambrex, Verviers, Belgium) supplemented with pasteurized plasma protein solution (Sanquin, Amsterdam, The Netherlands) and subjected to density gradient centrifugation using 70% Percoll (Amersham Pharmacia Biotech, Uppsala, Sweden) or 70% PureSperm (Nidacon, Gothenburg, Sweden) (650 *g* for 10 min). Then the pellet was washed once with culture medium (180 *g* for 10 min) and, depending on the sperm concentration, resuspended in 1–2 ml of culture medium. The sample was then incubated for 1 h at 37°C/5% CO_2 during which the motile spermatozoa were allowed to swim to the bottom of the tube ('swim-down'). Finally, the pellet was washed again (180 *g* for 10 min) and the volume, concentration and motility were assessed and the post-wash TMC was calculated. All measurements were performed with the Makler counting chamber (Sefi-Medical Instruments, Haifa, Israel).

Data analysis

All analyses were performed at cycle level, i.e. each cycle was considered as a separate unit of analysis. All cycles that resulted in an insemination were included in the analysis. For each of the continuous variables female age, male age, duration of subfertility and the semen parameters, it was assessed whether the association with the occurrence of pregnancy was linear or not. In each of these continuous variables, a spline function was constructed to assess the association between the variables and the occurrence of ongoing pregnancy (Harrell *et al.*, 1988). A spline function expresses the probability of pregnancy as a function of the continuous variable and is constructed using logistic regression analysis. Based on these spline functions, linearity was assessed and in absence of linearity the continuous variables were redefined where necessary, taking into account the association between these variables and the occurrence of pregnancy.

Subsequently, the potential prognosticators for IUI outcome