



## Article

# Predictive value of different covariates influencing pregnancy rate following intrauterine insemination with homologous semen: a prospective cohort study

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## KEY MESSAGE

Clinical pregnancy rates following homologous intrauterine insemination are significantly influenced by female age, male smoking, primary/secondary infertility and inseminating motile count. Based on the results of the final multivariate model, we were able to build a calculation tool for the prediction of clinical pregnancy for a given patient.

## ABSTRACT

The aim was to examine the value of different covariates in the prediction of intrauterine insemination (IUI) success. Between July 2011 and September 2015, data from 1401 IUI cycles with homologous semen in 556 couples were collected prospectively, by questionnaire, in a tertiary referral infertility centre. Statistical analysis was performed using generalized estimating equations (GEEs). GEEs were used instead of an ordinary logistic regression model to take into account the correlation between observations from the same person. The primary outcome parameter was clinical pregnancy rate (CPR), confirmed with a gestational sac and fetal heartbeat on ultrasonography at 7–8 weeks. An overall CPR of 9.5% per cycle was observed. Univariate statistical analysis revealed female and male age, male smoking, female body mass index, ovarian stimulation and inseminating motile count (IMC) as covariates significantly influencing CPR per cycle. Multivariate GEE analysis revealed that the only valuable prognostic covariates included female age, male smoking and infertility status (i.e. primary/secondary infertility). IMC showed a significant curvilinear relationship, with first an increase and then a decrease in pregnancy rate.

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## Introduction

Homologous intrauterine insemination (IUI) is generally used as a first-line treatment for couples with subfertility due to ejaculatory disorders, cervical factor infertility, moderate male factor and unexplained infertility.

For years there has been an ongoing search for predictive factors influencing successful ongoing pregnancy rates after IUI. Multiple studies have reported on the impact of factors such as female age [Arici et al., 1994; Badawy et al., 2009; Campana et al., 1996; Dinelli et al., 2014; Dorjpurev et al., 2011; Hendin et al., 2000; Karabinus and Gelety, 1997; Khalil et al., 2001; Montanaro Gauci et al., 2001; Stone et al., 1999; Tay et al., 2007], duration of infertility [Goverde et al., 2000; Tomlinson et al., 1996], type of infertility [Karabinus and Gelety, 1997; Khalil et al., 2001; Montanaro Gauci et al., 2001; Tay et al., 2007], hormone levels (i.e. FSH, oestradiol, progesterone) [Yavuz et al., 2013], use of different ovarian stimulation protocols [Arici et al., 1994; Cohlen et al., 1998, 2000; Guzik et al., 1999; Karabinus and Gelety, 1997; Khalil et al., 2001; Martinez et al., 1990; Nulsen et al., 1993], timing/induction of ovulation [Deaton et al., 1997; Khalil et al., 2001; Zreik et al., 1999], number of pre-ovulatory follicles [Khalil et al., 2001; Montanaro Gauci et al., 2001; Stone et al., 1999; Tomlinson et al., 1996; Yavuz et al., 2013], endometrial thickness by the time of ovulation [Khalil et al., 2001; Tomlinson et al., 1996], frequency of insemination (single or double) [Ragni et al., 1999; Ransom et al., 1994; Silverberg et al., 1992], sperm parameters (i.e. concentration [Montanaro Gauci et al., 2001], progressive motility [Hendin et al., 2000; Montanaro Gauci et al., 2001; Stone et al., 1999; Tomlinson et al., 1996; Yavuz et al., 2013; Zhao et al., 2004], morphology [Karabinus and Gelety, 1997; Lindheim et al., 1996; Matorras et al., 1995; Montanaro Gauci et al., 2001; Toner et al., 1995; Zhao et al., 2004], total motile sperm count [TMSC] [Campana et al., 1996; Ok et al., 2013; Tay et al., 2007; van der Westerlaken et al., 1998], inseminating motile count [IMC] [Arici et al., 1994; Khalil et al., 2001; Ombelet et al., 1997a; Stone et al., 1999]) and sperm washing procedures [Carrell et al., 1998; Dodson et al., 1998; Karabinus and Gelety, 1997; Stone et al., 1999]. Also the influence of body mass index (BMI) [Yavuz et al., 2013] and smoking habits [Farhi and Orvieto, 2009] on IUI outcome have been studied before. However, results on the predictive value of these parameters remain highly contradictory.

The vast majority of studies performed in the past are retrospective cohort studies, which has led to a great variation in outcome results because of differences in patient selection criteria, presence of various infertility factors, use or non-use of different ovarian stimulation protocols, number of inseminations per treatment cycle, number of cycles performed, methods of timing ovulation, sites of insemination, sperm parameters and sperm preparation techniques. Furthermore, because most studies are based on small patient populations and because clinical pregnancy rates (CPRs) per cycle with IUI are generally low, interpretation of study results is complicated and results vary. Therefore, controversy remains about the effectiveness of IUI, especially in relation to more refined techniques such as IVF and intracytoplasmic sperm injection (ICSI).

This study aimed to prospectively evaluate the extent to which the pregnancy outcome after homologous IUI is influenced by certain covariates such as age, smoking habits, BMI, infertility status, ovarian stimulation method, easy or difficult insemination, and sperm quality parameters. Covariates taken into account for our study were based

on a thorough review of the literature [Ombelet et al., 2014] and our personal experience.

## Materials and methods

### Patients

During the period between 1 July 2011 and 30 September 2015, the medical records of 556 subfertile couples, who received a total of 1401 homologous IUI cycles, were reviewed prospectively in a tertiary referral infertility centre. During the 20 min of mandatory bed rest following IUI [Custers et al., 2009; Saleh et al., 2000], a midwife sat next to the patient to review together all possible contributing factors by means of a questionnaire. On a monthly basis, the results of the questionnaires were examined for possible lack of data. Institutional Review Board approval was obtained for this study on 31 May 2013 (reference number: 13/054U).

All couples had been trying unsuccessfully to conceive for at least one year. Prior to IUI treatment, female patients were subjected to an infertility work-up, including medical history, physical examination, pelvic ultrasound, serum hormone assays between day 2 and 4 of the menstrual cycle, ultrasound monitoring of folliculogenesis, ovulation assessment by mid-luteal phase concentrations of progesterone in women with regular cycles, and a mid-cycle post-coital test. Hysterosalpingography (HSG) and/or laparoscopy was used to assess the uterine cavity and presence of at least one patent tube. In cases of a suspected tubal or uterine abnormality, a hysteroscopy and/or laparoscopy was performed. In all men at least two sperm examinations, microbiological tests and analysis of anti-sperm antibodies (ASA) were performed. All couples were tested for hepatitis B and hepatitis C virus before receiving any treatment. Couples suffering from unexplained infertility, mild endometriosis, oligo-/anovulation and moderate male factor infertility, with at least one patent Fallopian tube and an IMC of >1 million were considered eligible for IUI treatment. IUI cycles with use of frozen semen or escape IUI cycles, i.e. couples allocated to IVF/ICSI treatment who received escape IUI treatment because of low response to ovarian stimulation, were excluded from the study.

### Covariates

Covariates taken into account included female and male age (years), smoking (non-smoking, 1–14 cigarettes a day, ≥15 cigarettes a day), BMI (kg/m<sup>2</sup>), primary/secondary infertility, cycle number, ovarian stimulation method [natural cycle (NC), clomiphene citrate (CC), human menopausal gonadotrophin (HMG)/recombinant FSH (rFSH)], day (D) 0 oestradiol (ng/l) and progesterone (µg/l) levels, abstinence period (days), human chorionic gonadotrophin (HCG)-insemination time interval (hours), easy or difficult insemination [easy-clamp (C), easy+C, difficult+C, difficult+C+dilator, intracervically], occurrence of blood loss after insemination and sperm quality parameters [i.e. volume (ml), concentration (million/ml), total count (million), motility grade A (%), motility grade A+B (%), TMSC grade A (million), TMSC grade A+B (million), morphology (%), ASA (no factor, 10–50%, >50%) and IMC (million)].

### Ovarian stimulation

Patients were treated in a natural cycle in case of regular cycles. Ovarian stimulation with CC or HMG/rFSH protocols was used in cases

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