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ARTICLE

Pregnancy rates with intrauterine insemination: comparing 1999 and 2010 World Health Organization semen analysis norms

J Papillon-Smith [a,*], SE Baker [b], C Agbo [c], MH Dahan [a]

[a] *Department of Obstetrics and Gynecology, McGill University, 687 Pine Ave West, Montreal, QC, Canada H3A 1A1*; [b] *High School Student Summer Research Rotation, Stanford Medical School, 291 Campus Drive, Li Ka Shing Building, 3rd floor, Stanford, CA, USA*; [c] *Stanford University School of Medicine, 291 Campus Drive, Li Ka Shing Building, 3rd floor, Stanford, CA, USA*

* Corresponding author. *E-mail address:* jessica.papillon-smith@mail.mcgill.ca (J Papillon-Smith).

Dr Jessica Papillon-Smith is a fourth year resident specializing in Obstetrics and Gynecology at the McGill University Health Center, where she also obtained her Medical Degree. She has a particular interest in reproductive medicine. Dr Michael Haim Dahan, senior author on this submission, is an Assistant Professor in the Department of Obstetrics and Gynecology at McGill University. He specializes in Reproductive Endocrinology and Infertility at the McGill University Health Center, where public, free access to fertility treatments allows very large numbers of patients to receive reproductive care each year.

Abstract Over the past 30 years, The World Health Organization has serially measured norms for human sperm. In this study, 1999 and 2010 semen analysis norms as predictors of pregnancy were compared during intrauterine insemination (IUI). A retrospective cohort study was conducted using data collected from the Stanford Fertility Center, between 2005 and 2007, with 981 couples undergoing 2231 IUI cycles. Collected semen was categorized according to total motile sperm counts (TMSC): 'normal (N.) 1999 TMSC', 'abnormal (AbN.) 1999/N. 2010 TMSC', or 'AbN. 2010 TMSC'. Sample comparison was also based on individual semen parameters: 'N. 1999 WHO', 'AbN. 1999/N. 2010 WHO', or 'AbN. 2010 WHO'. Pregnancy (defined by beta-HCG concentration) rates were calculated. Data were compared using correlation coefficients, t-tests and chi-squared tests, with and without adjusting for confounders. Pregnancy rate comparison based on TMSC ('N. 1999 TMSC', 'AbN. 1999/N. 2010 TMSC' and 'AbN. 2010 TMSC') showed a negative correlation ($r = -0.41$, $P = 0.05$). Pregnancy rate did not differ when comparisons were based on the presence of abnormal parameters, even when controlling for confounders. Therefore, TMSC based on the 1999 parameters shows best correlation with pregnancy rate for IUI; updating these norms in 2010 has little clinical implication in infertile populations.

KEYWORDS: intrauterine insemination, male factor infertility, pregnancy rate, semen analysis, World Health Organization

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Introduction

Intrauterine insemination (IUI) is an assisted reproduction technique that has proven, over the years, to be an effective, relatively inexpensive and non-invasive first-line treatment for couples suffering from various types of infertility (Campana et al., 1996; Dickey et al., 1999; Goverde et al., 2000; Guzick et al., 2001; Van Voorhis et al., 2001; Duran et al., 2002a; Ombelet et al., 2014). Multiple trials have established the efficacy of IUI in treating different fertility issues; however, its value in the treatment of male factor subfertility has been debated (Martinez et al., 1993; Campana et al., 1996; Guzick et al., 2001; Van Voorhis et al., 2001). Indeed, in a randomized controlled trial, Goverde et al. (2000) concluded that IUI was as effective a treatment in those suffering from idiopathic infertility as it was for those with a predominant male-factor issue; Hughes (1997), however, in a meta-analysis established that couples with male-factor subfertility experienced pregnancy rates with IUI that were only one-half of those with unexplained infertility.

These opposing conclusions likely stem from different definitions of male-factor subfertility, with varying semen analysis limits used as norms. This also suggests that a certain threshold phenomenon exists wherein specific couples with male factor infertility are likely to benefit from insemination, whereas others should bypass this treatment option and proceed to more complex methods of assisted reproduction, such as IVF with intracytoplasmic sperm injection (ICSI) (Goverde et al., 2000).

To ascertain which couples affected by male-factor subfertility might benefit from artificial insemination, the value of various semen parameters in predicting the success of IUI have been investigated (Montanaro Gauci et al., 2001; Ombelet et al., 2014). The total motile sperm count (TMSC) is the product of semen volume, sperm motility and its concentration. Because of its incorporation of multiple semen analysis elements, the TMSC is thought to be a key determinant in the success of insemination (Brasch et al., 1994; Campana et al., 1996; Dickey et al., 1999; Duran et al., 2002a, 2002b; Horvath et al., 1989; Miller et al., 2002; Ombelet et al., 2014; Van Voorhis et al., 2001; Wainer et al., 2004; Yalti et al., 2004). In fact, a systematic review published in 2014 by Ombelet et al. (2014) scrutinized the literature for the semen qualities predictive of IUI success in male factor infertility and established that the TMSC was a tool with substantial discriminative ability.

For more than 30 years, the World Health Organization (WHO) has evaluated such parameters and has serially calculated norms for human semen, which are typically used to define the lower limits of male fertility (Cooper et al., 2010; World Health Organization, 1987, 1992, 1999). Manuals for the laboratory examination of semen are periodically published; the first being released in 1980, followed by updates in 1987, 1992 and 1999 (Cooper et al., 2010; World Health Organization, 1987, 1992, 1999). In 2010, the WHO convened new reference values for semen analysis that are lower than previously described (Cooper et al., 2010). A novelty in this edition is that the distributions for semen characteristics were obtained by analysing the semen results of men from around the world, whose partners had a time to pregnancy of less than 12 months. Using these results, one-sided lower reference limits were determined (fifth centile) and suggested as the lower thresholds for normalcy (Cooper et al., 2010). These parameters include a minimum semen volume of 1.5 ml or more (previously ≥ 2 ml), a total sperm number of 39 million or more per ejaculate (previously ≥ 40 million), a sperm concentration of 15 million per ml (previously ≥ 20 million per ml), a motility of of 40% or over (not previously included), a forward motility of 32% or more (previously ≥ 50%), and a 4% or more normal sperm morphology (previously 14%) (Cooper et al., 2010; World Health Organization, 1987, 1992, 1999). Some might argue that these poorer parameters reflect a global, gradual decline in semen quality owing to a variety of environmental factors or to new and worsening metabolic and endocrine pathologies (Adamopoulos et al., 1996; Auger et al., 1995). This variation, however, may be better explained by a methodological bias wherein laboratories adhere to more stringent quality-control standards. Irrespectively, by applying these new norms, the WHO aims to decrease the misdiagnosis of infertility and improve overall clinical care (Cooper et al., 2010).

One would expect that lowering the limits of semen characteristics would translate into decreased pregnancy rates with intrauterine insemination, particularly if these norms are used for treatment planning in an infertile population. The goal of this study is to evaluate whether the 2010 semen analysis parameters are, in fact, better predictors of IUI success than were the 1999 limits.

Materials and methods

All couples undergoing IUI at the Stanford University Fertility Center during a 30-month period were retrospectively enrolled into our database for evaluation of semen quality on the day of insemination. The data were collected between 2005 and 2007. A total of 981 couples underwent 2231 IUI cycles.

First, semen quality was classified into three groups based on the TMSC; pre-processing of the specimen. These groups were as follows: (i) normal TMSC per the 1999 WHO parameters ('normal (N.) 1999 TMSC') = 2 ml × 20 million/ml × ≥50% forward motility, which equals a minimum of 20 million forward motile sperm; (ii) abnormal TMSC by the 1999 WHO parameters, but normal by the 2010 parameters ('abnormal (AbN.) 1999/N. 2010 TMSC') = 7.2 to 19.999 million forward motile sperm; and (iii) abnormal TMSC per the 2010 WHO parameters ('AbN. 2010 TMSC') = 1.5 ml × 15 million/ml × 32% forward motility, which is less than 7.2 million forward motile sperm.

This amounted to 1604 inseminations amongst the 'N. 1999 TMSC' parameter group, 362 inseminations amongst the 'AbN. 1999/N. 2010 TMSC' group and 265 inseminations amongst the 'AbN. 2010 TMSC' group.

Forward motility was selected as a study parameter rather than overall motility for a few reasons. First, the 1999 WHO semen analysis parameters only include forward motility; therefore, this parameter was also selected for the 2010 WHO data, so that all specimens could be properly compared. Second, it seems unlikely that static motility contributes to fertilization as significantly as forward motility does.

Next, TMSC was used as a study parameter rather than the minimum sperm count measured by the WHO. Although 1.5 ml × 15 million/ml are the numbers used to calculate the 2010 normal TMSC, this is stricter that the minimum 39 million