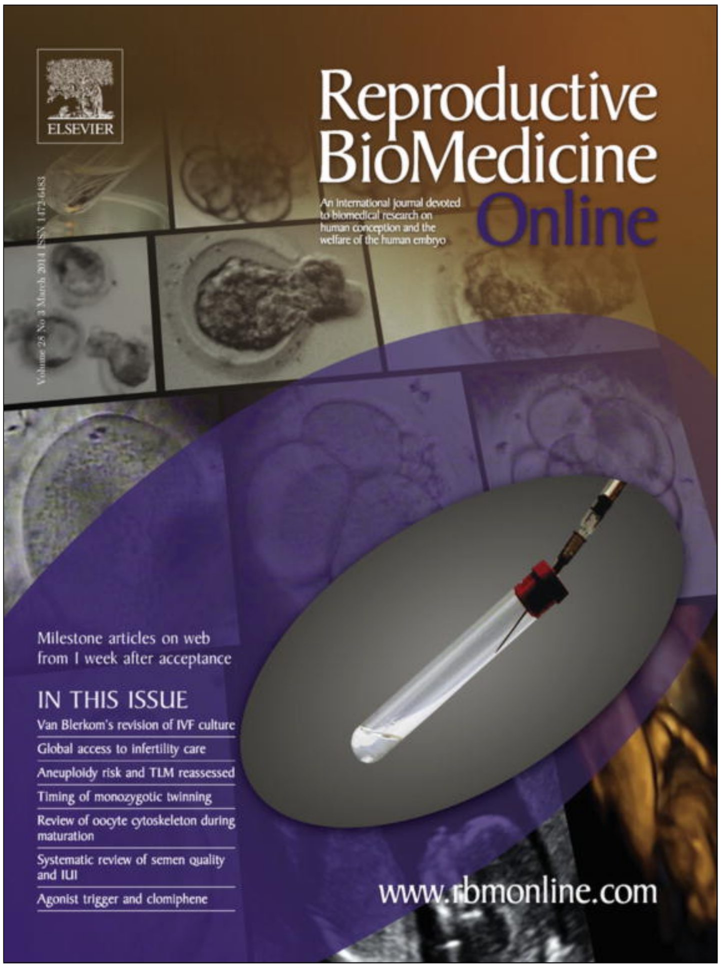
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MINI-REVIEW

Semen quality and prediction of IUI success in male subfertility: a systematic review

Willem Ombelet [a,b,*], Nathalie Dhont [a], Annelies Thijssen [a,b], Eugene Bosmans [a], Thinus Kruger [c]

[a] *Genk Institute for Fertility Technology, Department of Obstetrics and Gynaecology, Genk, Belgium;* [b] *Faculty of Medicine and Life Sciences, Hasselt University, Martelarenlaan 42, Hasselt, Belgium;* [c] *Reproductive Biology Unit, Department of Obstetrics and Gynaecology, Stellenbosch University and Tygerberg Hospital, Tygerberg, South Africa*
[*] Corresponding author. *E-mail addresses:* willem.ombelet@telenet.be, willem.ombelet@zol.be (W Ombelet).

Willem Ombelet started his career researching infertility and IVF in 1984 in Pretoria, South Africa. In 1998, he obtained his PhD at the University of Leuven on 'The value of sperm morphology and other semen parameters in diagnosis and treatment of human subfertility'. He became the head of the department of obstetrics and gynaecology in Genk in 1999. From 2001 until 2004, he was the President of the Flemish Society of Obstetrics and Gynaecology. Dr Ombelet is the founder of the Genk Institute for Fertility Technology and the Walking Egg Foundation. Since 2006, he has been the co-ordinator of the ESHRE Special Task Force 'Developing countries and infertility'.

Abstract Many variables may influence success rates after intrauterine insemination (IUI), including sperm quality in the native and washed semen sample. A literature search was performed to investigate the threshold levels of sperm parameters above which IUI pregnancy outcome is significantly improved and/or the cut-off values reaching substantial discriminative performance in an IUI programme. A search of MEDLINE, EMBASE and Cochrane Library revealed a total of 983 papers. Only 55 studies (5.6%) fulfilled the inclusion criteria and these papers were analysed. Sperm parameters most frequently examined were: (i) inseminating motile count after washing: cut-off value between 0.8 and 5 million; (ii) sperm morphology using strict criteria: cut-off value ≥5% normal morphology; (iii) total motile sperm count in the native sperm sample: cut-off value of 5–10 million; and (iv) total motility in the native sperm sample: threshold value of 30%. The results indicate a lack of prospective studies, a lack of standardization in semen testing methodology and a huge heterogeneity of patient groups and IUI treatment strategies. More prospective cohort trials and prospective randomized trials investigating the predictive value of semen parameters on IUI outcome are urgently needed.

KEYWORDS: assisted reproduction, intrauterine insemination, predictive value, pregnancy rate, semen, sperm quality

Introduction

Intrauterine insemination (IUI) is a simple and noninvasive technique which can be performed without expensive infrastructure with a reasonable cumulative live birth rate within three or four cycles (Cohlen, 2005). The rationale behind artificial IUI is increasing the gamete density at the site of fertilization. IUI has been proven to be easier to perform, less invasive and less expensive than other more complex methods of assisted reproduction (Ombelet et al., 1995). Risks are minimal provided that the multiple gestation incidence can be reduced to an acceptable level and efforts are

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made to decrease horizontal transmission of sexually transmitted infections, including HIV.

Increasing interest in IUI is undoubtedly associated with the refinement of techniques for the preparation of washed motile spermatozoa (Boomsma et al., 2007; Loskutoff et al., 2005). Semen washing procedures can remove prostaglandins, infectious agents, antigenic proteins, nonmotile spermatozoa, leukocytes and immature germ cells. This may enhance sperm quality by decreasing the formation of free oxygen radicals after sperm preparation. The final result is an improved fertilizing capacity of the spermatozoa *in vitro* and *in vivo*.

Despite the extensive literature on IUI and due to a lack of good-quality prospective cohort trials, controversy remains about the effectiveness of this treatment procedure, particularly in relation to IVF and intracytoplasmic sperm injection (ICSI; Bensdorp et al., 2007; Cohlen, 2005; ESHRE Capri Workshop Group, 2009; Ombelet, 2005; Pashayan et al., 2006). This may be explained by the fact that most studies are retrospective and not only vary in the comparison of the study group (different groups of male subfertility) but also in the use or non-use of different ovulation induction regimens, the number of inseminations per treatment cycle, methods of timing ovulation, sites of insemination, methods of sperm preparation and use of additives such as kallikrein, platelet-activating factor and antioxidants, as shown in **Figure 1**.

According to the new and updated recommendations published in the NICE clinical guidelines, IUI is not recommended anymore for unexplained and mild male factor infertility (NICE guidelines, 2013): 'For people with unexplained infertility, mild endometriosis or ''mild male factor infertility'', who are having regular unprotected sexual intercourse, it is advised not to offer IUI routinely, either with or without ovarian stimulation, but advise them to try to conceive for a total of 2 years before IVF will be considered'.

Despite the NICE recommendations, it can be expected that artificial insemination with husband's semen remains a widely used treatment option for many couples with unexplained infertility, cervical factor subfertility, physiological or psychological sexual dysfunction and mild-to-moderate male subfertility.

To find out which couples can benefit from IUI in the case of male subfertility, the power of different semen parameters in predicting success after IUI need to be investigated. Although the World Health Organization (WHO) tried to standardize the performances of semen analysis and related procedures in order to reduce variation in the results obtained, a literature search on this topic is frustrating due to the ongoing lack of standardization of interpretation of semen results (Tomlinson, 2010).

This structured review aimed to investigate the accuracy of sperm parameters in predicting IUI success. Therefore, threshold levels of sperm quality above which IUI pregnancy outcome is significantly improved were examined. Secondly, the cut-off values reaching substantial discriminative performance considering IUI outcome were investigated. For the current systematic review, no written protocol was registered.

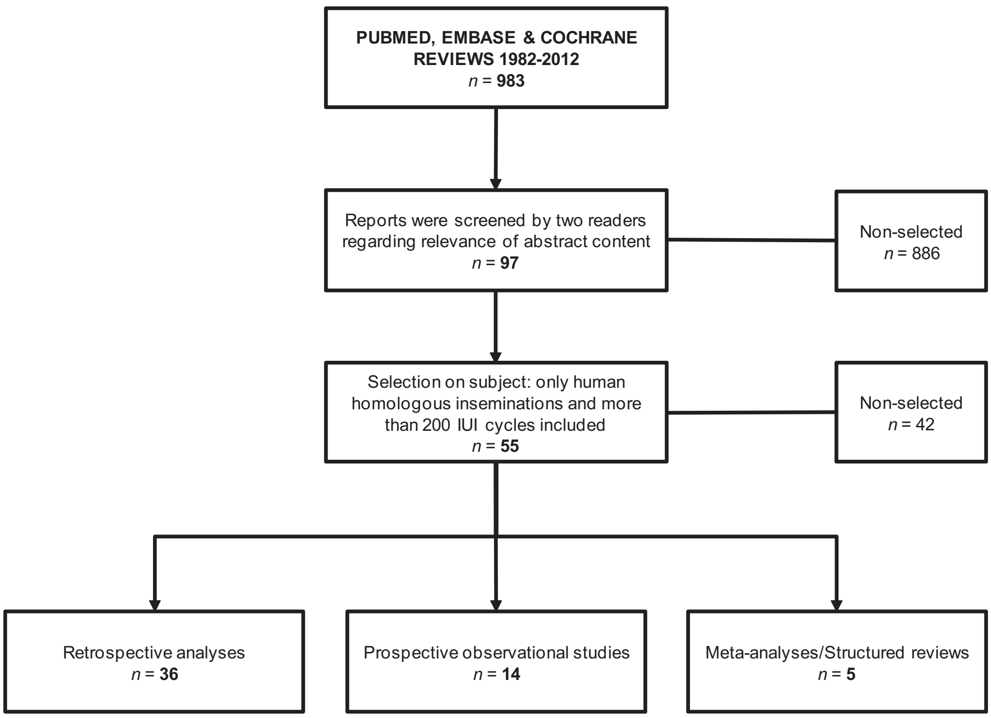

Figure 1 Factors influencing the success rate of artificial intrauterine insemination with homologous spermatozoa. CC = clomiphene citrate; HCG = human chorionic gonadotrophin; HMG = human menopausal gonadotrophin; IUI = intrauterine insemination; rec FSH = recombinant FSH.

Materials and methods

Search strategy

By means of a computerized MEDLINE search, the literature for a 31-year period, from January 1982 until December 2012, was reviewed. The following search terms were used: (success OR outcome OR pregnancy OR predictive value) AND (semen OR spermatozoa) AND (IUI OR intrauterine insemination OR artificial insemination). Other relevant studies were identified by searching EMBASE using the same search terms and Cochrane Controlled Trial register published until December 2012. The reference lists of all selected articles were examined to identify papers that were not captured by the electronic search and the 'related articles' function of PubMed was also used. There was no language restriction and the identification of relevant studies was performed independently by two authors (WO and ND).

Study inclusion criteria and data extraction

Studies were only included if the authors reported on the value of sperm parameters on the prediction of IUI success in couples with male subfertility. Only studies with a minimum of 200 IUI cycles using homologous spermatozoa were included.

Male subfertility was defined as semen quality below the standards of WHO during that specific period. Studies in a population with unexplained infertility and studies reporting on results in a sperm donor programme were excluded.

The outcome most frequently used was clinical pregnancy defined as a pregnancy confirmed by a gestational sac and/or fetal heart activity on ultrasound. Nowadays, results should be expressed as live birth rates (or at least ongoing pregnancy rates) per couple applying intention to treat analysis, but these outcome parameters were not used in the selected studies.

Results

In the Cochrane Library, 10 reviews could be selected, but none of these evaluated the predictive value of semen parameters on IUI outcome. The EMBASE and MEDLINE search revealed a total of 983 papers. Only 55 studies (5.6%) fulfilled the inclusion criteria and these papers were analysed (Table 1 and Figure 2). In the majority of IUI studies, the predictive value of sperm parameters was not investigated at all; in many other studies, quality assurance associated with semen analysis and a successful service, as indicated by acceptable pregnancy rates, was clearly not available.

Out of the 55 selected studies, 36 papers performed a retrospective analysis and 14 articles described the results of a prospective observational study. Five structured reviews and/or meta-analyses were obtained.

In the meta-analysis of Van Waart et al. (2001), six studies yielded a risk difference between the pregnancy rates achieved in the patients below and above the 4% strict sperm morphology criteria threshold of −0.07 (95% CI −0.11 to 4.03; $P < 0.001$). In the meta-analysis of 16 studies by Van Weert et al. (2004), receiver operating characteristics (ROC) curves indicated a reasonable predictive performance towards IUI outcome for the inseminating motile count (IMC). At cut-off levels between 0.8 and 5 million, the specificity of the IMC, defined as the ability to predict failure to become pregnant, was as high as 100%; the sensitivity of the test, defined as the ability to predict pregnancy, was limited.

According to Ombelet et al. (1997a, 2003), an IMC of 1 million can be used as a reasonable threshold level above which IUI can be performed with acceptable pregnancy rates. Overall, sperm morphology and IMC, as an individual parameter, were of no prognostic value using ROC curve analysis. Sperm morphology turned out to be a valuable prognostic parameter in predicting IUI success if the IMC was <1 million (area under ROC curve 77.6%). The cumulative live birth rate (CLBR) after three IUI cycles was 13.6% if the IMC was <1 million, significantly different from the group with an IMC >1 million (22.4%, $P < 0.05$). Considering only patients with IMC <1 million and sperm morphology >4%, the CLBR was 21.9%, comparable with the CLBR of all cycles with an IMC of >1 million (Ombelet et al., 1997a).

In the systematic review of Castilla et al. (2010), investigating the clinical value of the sperm chromatin structure assay (SCSA) and classical semen parameters, it was shown that in couples treated with IUI the clinical validity was higher for SCSA compared with sperm morphology, with a positive likelihood ratio (LR+) of 6.1 (95% CI 2.6–14.6) and 1.9 (95% CI 1.1–3.0) for SCSA and sperm morphology, respectively. They also concluded that, despite this finding, the clinical value of SCSA was not enough to introduce this parameter as a routine test in male infertility work up.

The four sperm parameters that were most frequently examined and cited were the following: (i) IMC; (ii) sperm morphology using strict criteria; (iii) total motile sperm count in the native sperm sample (TMSC); and (iv) total motility in the native sperm sample (TM) (Table 1).

In 24 articles, the IMC was cited as an important predictive parameter, in seven out of 20 studies, a cut-off value of 1 million was mentioned, in four studies a cut-off values of between 1 and 2 million was used and in four studies, the authors calculated a threshold value of 5 million.

Sperm morphology using strict criteria was the second most cited sperm parameter. In 11 out of 16 studies, ≥5% normal forms was reported as the best cut-off value to predict IUI outcome. When utilizing these cut-off values of sperm morphology and IMC, there is poor sensitivity for predicting who will conceive but a high specificity for predicting failure to conceive with IUI.

TMSC was also reported to be an important predictive parameter in 12 papers with a cut-off value of 5 million in three papers and 10 million in six papers. A TM threshold value of 30% was found in three out of six articles in which TM was found to be a good predictor of success.

Other semen parameters less frequently cited were the initial concentration of the native sperm sample, SCSA, the DNA-fragmentation index, computer-assisted sperm analysis parameters and the Hemizona index.

Discussion

Most selected studies in this search are retrospective and not only vary in the comparison of the study group (different

Table 1 Overview of papers examining and reporting on the influence of sperm quality on IUI outcome (1982–2011).

Publication	*Country*	*Couples (n)*	*Cycles (n)*	*Sperm parameter*	*Threshold*	*Type of study*
Berker et al. (2012)	Turkey	338		Motility grade A/TMSC	>10 million if motility grade A=0	RA
Sun et al. (2012)	China	412	908	Morphology SC	≥5%	RA
Demir et al. (2011)	Turkey	212	253	TMSC	>10 million	RA
				Morphology SC	>4%	
Dorjpurev et al. (2011)	Japan	283	1177	TM	>30%	RA
				TMSC	>10 million	
Nikbakht and Saharkhiz (2011)	Iran	445	820	TMSC	5–10 million	POS
				IMC	>10 million	
				Morphology SC	≥5%	
Yang et al. (2011)	China	482		SCSA–DFI	<25%	POS
Youn et al. (2011)	China		383	CASA concentration	111 million	RA
				CASA motility grade AB	51.40%	
				CASA motility grade A	30.10%	
Castilla et al. (2010)	Spain			SCSA–DFI		Structured review
Merviel et al. (2010)	France	353	1038	TMSC	>5 million	RA
Tijani and Bhattacharya (2010)	UK			TMSC	>10 million	Structured review
Badawy et al. (2009)	Egypt	393	714	IMC	>5 million	POS
				Morphology WHO	>30%	
Haim et al. (2009)	France		248	Motility grade A	>10%	POS
De La Cuesta Benjumea et al. (2008)	Spain	183	500	IMC	>1.5 million	RA
Guven et al. (2008)	Turkey	232	255	Morphology SC	>4%	RA
Bungum et al. (2007)	Denmark		387	SCSA–DFI	≤30%	RA
Kdous et al. (2007)	Tunisia	138	206	IMC	>1.1 million	RA
Tay et al. (2007)	Malaysia	317	507	IMC/TMSC	>20 million	RA
Arslan et al. (2006)	USA	82	313	HZI	<30%	POS
Mehrannia (2006)	Iran	824	824	IMC	>10 million	RA
Grigoriou et al. (2005b)	Greece	615	1641	Morphology SC	>10%	RA
De La Cuesta et al. (2004)	Spain	168	430	IMC	>2 million	RA
Shibahara et al. (2004)	Japan	160	682	Morphology SC	>15.5%	POS
				CASA–RASP	≥25.5%	
van Weert et al. (2004)	the Netherlands			IMC	0.8–5 million	Meta-analysis
Wainer et al. (2004)	France	889	2564	IMC + Morphology WHO	>5 million/>30%	RA
Yalti et al. (2004)	Turkey	190	268	TM	>30%	RA
Zhao et al. (2004)	USA	431	1007	TM	>80%	RA
Makkar et al. (2003)	Hong Kong	292	600	IC	>20 million/ml	RA
				Morphology SC	≥7%	
				IMC	>1 million	
Ombelet et al. (2003)	Belgium			Morphology SC	>4%	Structured review
				IMC	>1 million	
Saucedo de la Llata et al. (2003)	Spain		787	Morphology WHO	>20%	RA
				IMC	>1 million	
Lee et al. (2002a)	China	209	244	Morphology SC	>4%	POS
Lee et al. (2002b)	Singapore	1479	2846	IMC	>1 million	RA
				TM	>30%	
Miller et al. (2002)	USA	438	1114	IMC	>10 million	POS
Hauser et al. (2001)	Israel	108	264	Morphology SC	>4%	POS
Khalil et al. (2001)	Denmark	893	2473	IMC	>5 million	RA
Montanaro Gauci et al. (2001)	South Africa		495	Morphology SC	>4%	RA

(*continued on next page*)

Table 1 *(continued)*

Publication	*Country*	*Couples (n)*	*Cycles (n)*	*Sperm parameter*	*Threshold*	*Type of study*
Van Voorhis et al. (2001)	USA	1039	3479	TMSC TM	>10 million >50%	RA
Van Waart et al. (2001)	South Africa			Morphology SC	>4%	Structured review
Branigan et al. (1999)	USA	414	1100	IMC Sperm survival 24 h	≥10 million ≥70%	POS
Dickey et al. (1999)	USA	1841	4056	Motility grade AB TC TMSC	≥30% ≥10 million ≥5 million	RA
Stone et al. (1999)	USA		9963	TMSC TM	≥4 million ≥60%	RA
Cohlen et al. (1998)	The Netherlands	74	308	TMSC	>10 million	POS/RCoT
Shulman et al. (1998)	Israel	160	544	Semen parameters	Not useful	RA
Van der Westerlaken et al. (1998)	The Netherlands	566	1763	IMC	>10 million	RA
Berg et al. (1997)	Germany	902	3037	IMC	>0.8 million	RA
Karabinus and Gelety (1997)	USA	193	538	Morphology SC	Not useful	RA
Ombelet et al. (1997a)	Belgium	373	792	IMC and Morphology SC	>1 million + >4%	RA
Burr et al. (1996)	Australia	163	330	Morphology SC IMC	>10% Not useful	RA
Campana et al. (1996)	Switzerland	332	1115	IMC	>1 million	POS
Huang et al. (1996)	China	939	1375	IMC	>5 million	POS
Ombelet et al. (1996)	Belgium	412	1100	Morphology SC	≥4%	RA
Matorras et al. (1995)	Spain	74	271	Morphology SC	Not useful	POS
Toner et al. (1995)	USA	126	395	IMC Morphology SC	>2 million >4%	RA
Brasch et al. (1994)	USA	546	1205	IMC	>20 million	RA
Francavilla et al. (1990)	Italy	86	411	Morphology WHO TMSC	>50% >5 million	RA
Horvath et al. (1989)	USA	232	451	IMC	>1 million	RA

CASA = computer-assisted sperm analysis; DFI = DNA fragmentation index; HZI = Hemizona index; IC = initial concentration in native sperm sample; IMC = inseminating motile count or post-wash total motile sperm count; POS = prospective observational study; RA = retrospective analysis; RCoT = randomized crossover trial; SC = strict criteria; SCSA = sperm chromatin structure assay; TM = total motility in native sperm sample; TMSC = total motile sperm count in native sperm sample; WHO = World Health Organization criteria.

groups of male subfertility) but also in the use or non-use of different ovulation induction regimens, the number of inseminations per treatment cycle, methods of timing ovulation, methods of sperm preparation and use of additives such as platelet-activating factor, pentoxifylline and antioxidants. All these factors may influence the impact of sperm quality on IUI success (Boomsma et al., 2007; Cantineau et al., 2007; Grigoriou et al., 2005a; Matorras et al., 2004; Said and Land, 2011). The most important determinant regarding IUI outcome is undoubtedly the use of ovarian stimulation protocols and, in particular, multifollicular development. According to the meta-analysis of van Rumste et al. (2008), multifollicular growth is associated with increased pregnancy rates in IUI with ovarian stimulation, but at the expense of an increased multiple pregnancy rate. The authors also stated that the presence of three or four follicles was associated with an increased multiple pregnancy rate without substantial gain in overall pregnancy rate. They concluded that IUI with ovarian stimulation should not aim for more than two follicles. One stimulated follicle should be the goal if safety is the primary concern, whereas two follicles may be accepted after careful patient counselling.

Also, the duration of subfertility and the female age differed tremendously between studies or were not mentioned at all, although these factors are well recognized to be associated with IUI success, indirectly influencing the impact of semen quality as a predictor of IUI outcome.

Another confounding factor when interpreting these data is the wide and complex variation in methods of sperm preparation and semen testing methodology. A uniform approach in the interpretation of seminal parameters is mandatory, the best example being the persistent variance in sperm morphology scoring between and even within laboratories (Ombelet et al., 1997b,c; Tomlinson, 2010). This ongoing error associated with inconsistent semen-testing methodologies means that many men at the margins of treatment decision making can wrongly be excluded, or conversely men are sometimes included who perhaps should not be.

As a result of this literature search, the calculations are based on evidence levels 2 or 3. Nevertheless, it seems that

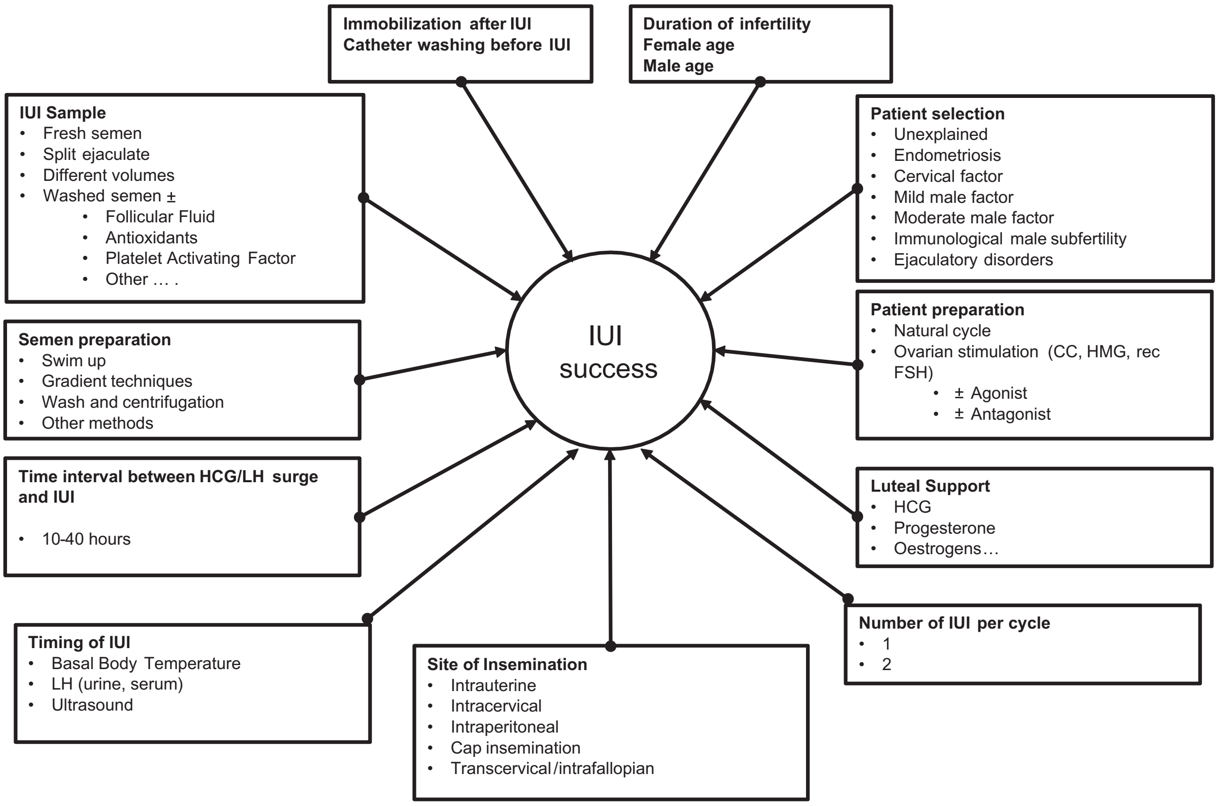

Figure 2 Overview of the systematic literature search concerning the prognostic value of sperm quality parameters in an intrauterine insemination programme.

the following cut-off values can be used when talking about semen parameters with an important and substantial discriminative performance in an IUI programme: IMC >1 million, sperm morphology using strict criteria >4%, TMCS of 5–10 million and TM of >30%. When using these cut-off levels, the ability to predict pregnancy was limited (poor sensitivity) for all parameters, but the specificity defined as the ability to predict failure to become pregnant was much better.

The results also do not mean that below these cut-off levels IUI can't be used as a good and effective first-line treatment in male subfertility cases, they only indicate that above these threshold levels the success rate after IUI seems to be significantly improved. When reviewing the literature, it is also clear that prewash semen parameters do not always reflect post-wash semen characteristics. Selecting a couple for IUI in male factor infertility cases includes the study of both pre- and post-wash semen characteristics before starting the IUI treatment.

The lack of large prospective cohort studies is easy to understand. Because natural-cycle IUI and clomiphene citrate stimulation are frequently used in IUI programmes, the budget for IUI studies is almost negligible when compared with the budget spent on other methods of assisted reproduction such as IVF and ICSI. Studies on the predictive value of sperm quality on IUI success supported and organized by the pharmaceutical industry are not available. It is obvious that the pharmaceutical industry is not really interested in performing good-quality studies at the moment. The lack of valuable studies can also partially be explained by the fact that a lot of IUI procedures are performed as a first-line therapy in non-IVF centres. The experience to perform scientific studies is mostly lower in these centres compared with university-based IVF centres. The results also give the impression that the majority of IVF centres are not really interested in performing prospective high-quality studies in the field of IUI. It should be investigated whether this finding can be explained by a conflict of interest amongst authors who advocate the use of IVF.

A nice example showing the discrepancy between theory (evidence-based medicine) and clinical practice is a study performed in 2002 by Miskry and Chapman. A postal survey was sent to 37 well-known fertility centres within Australia and New Zealand to establish current clinical IUI practice. Although 80% of centres recognized considerable advantages to the patient in terms of risk/benefit ratio and financial cost associated with IUI compared with IVF in moderate male infertility cases, nearly a third of centres promoted IVF as first-line treatment even in the presence of patent tubes and normal semen. When semen parameters were reduced, IUI was rarely considered. According to the authors, it appears that evidence-based medicine is not yet translated into clinical practice in many units.

Nevertheless, from a societal point of view, considering the economical impact due to the indirect costs associated with IUI because of high rates of multiple pregnancies, well-organized randomized studies are urgently needed to define usable cut-off values for selecting couples for IUI in male subfertility cases, taking into account the cost-effectiveness of the different methods of assisted reproduction (Van Voorhis et al., 1997).

Looking to the future, a marked increase in pregnancy rates with IVF compared with IUI can be expected in general. A recent study modelling outcomes and costs showed that moving directly to IVF might be more cost-effective than starting with gonadotrophin-stimulated IUI for unexplained and mild male factor infertility (Bhatti and Baibergenova, 2008), but in this study only the short-term costs were included in the analysis. The costs of complications arising from multiple births were not included, although these costs are of crucial when talking about cost-effectiveness.

IUI is a simple and noninvasive technique with minimal monitoring and risks, at least if multiple pregnancy rates can be avoided. It can be performed without expensive infrastructure with a reasonable success rate within three or four cycles in most centres. IUI is undoubtedly a more patient-friendly strategy compared with IVF/ICSI (Pennings and Ombelet, 2007) and it has been shown that a substantial number of subfertile couples prefer to be treated in a patient-centred clinic rather than going to centres only focusing on success rates. A lack of patient-centredness was the most cited nonmedical reason for changing fertility clinics (van Empel et al., 2011).

Belgian data on IUI clearly show that, although the pregnancy rate per cycle is significantly higher in IVF/ICSI versus IUI, the price per delivery is significantly lower for IUI (BELRAP, 2011, 2012). For IUI, the live birth rate per insemination with husband's semen was 7.7%, taking into account that gonadotrophins were only used in 20% of IUI. In almost 30% of cases, IUI was performed in a natural cycle. The multiple pregnancy rate was 5.8% (twins 5.7%, triplet 0.1%). In the same year (2009), the live birth rate per oocyte recovery for IVF/ICSI was 19.8%, with a multiple pregnancy rate of 11.9% (twins 11.7%, triplet 0.2%). The calculated price per delivery, even not taking into account the higher multiple pregnancy rate for IVF/ICSI, was significantly lower for IUI compared with IVF/ICSI (Ombelet, unpublished data).

Nevertheless, when the difference in cumulative live birth rate per couple between IUI and IVF continues to increase, it will be very difficult to argue that IUI clinics are acting in the best interest of their patients. It's time for action: clinicians are obliged to increase pregnancy rates in IUI programmes by making use of different evidence-based strategies improving success rates. It has been proven that at least 10–15 min of immobilization should be applied after every IUI (Custers et al., 2009), which can result in significantly higher pregnancy rates in higher pregnancy rates compared with single IUI in couples with male factor subfertility (Cantineau et al., 2009; Liu et al., 2006). Oral antioxidants given to infertile men with high semen oxidative stress result in significant reduction in semen ROS (reactive oxygen species) and serum Inhibin B levels, significant increase in the sperm linear velocity and per cycle IUI pregnancy rates (Comhaire et al., 2005). Novel sperm selection methods have recently been developed, these methods aim at isolating mature, structurally intact and nonapoptotic spermatozoa with high DNA integrity (Said and Land, 2011), and their value needs to be investigated in IUI as well.

Until today, the balance of published studies still favours to start with IUI before moving to IVF in the treatment of mild and moderate male subfertility. It is time to realize that a better selection of those couples who benefit most from IUI as a first-line treatment is needed and therefore a better understanding of the effect of sperm quality on IUI success is mandatory. The prevalence of multiple births will become one of the most important determinants in deciding which treatment strategy has to be used, taking into account the economical restraints in most countries.

In conclusion, the literature did not reveal level 1 evidence on the relationship between sperm quality and IUI success. Although more prospective observational cohort studies and well-organized retrospective analyses are urgently needed, this structured review indicates that IMC >1 million with IUI is probably the best cost-effective treatment before starting IVF, irrespective of sperm morphology. More answers to the question as to when to perform IUI in male factor infertility cases will never be obtained until more multicentre prospective trials according to standard protocols are organized. Despite the current ongoing debate concerning cost-effectiveness of IUI versus IVF in moderate male factor infertility, other factors might be important, such as the well-known differences between both strategies in risk profile and patient satisfaction.

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