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REVIEW

High-magnification selection of spermatozoa prior to oocyte injection: confirmed and potential indications

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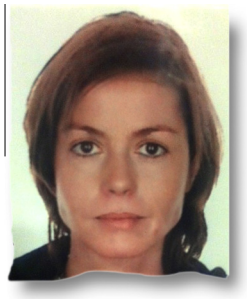

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Abstract Intracytoplasmic morphologically selected sperm injection (IMSI) involves the use of differential interference contrast microscopy at high magnification (at least ×6300) to improve the observation of live human spermatozoa (particularly by showing sperm head vacuoles that are not necessarily seen at lower magnifications) prior to intracytoplasmic sperm injection (ICSI) into the oocyte. However, a decade after IMSI's introduction, the technique's indications and ability to increase pregnancy and/or birth rates (relative to conventional ICSI) are subject to debate. In an attempt to clarify this debate, this work performed a systematic literature review according to the PRISMA guidelines. The PubMed database was searched from 2001 onwards with the terms 'IMSI', 'MSOME' and 'high-magnification, sperm'. Out of 168 search results, 22 relevant studies reporting IMSI outcomes in terms of blastocyst, pregnancy, delivery and/or birth rates were selected and reviewed. The studies' methodologies and results are described and discussed herein. In view of the scarcity of head-to-head IMSI versus ICSI studies, the only confirmed indication for IMSI is recurrent implantation failure following ICSI. All other potential indications of IMSI require further investigation.

KEYWORDS: human spermatozoa, IMSI, MSOME, outcome, pregnancy rate, vacuole

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Introduction

Since its first use in the early 1990s (Palermo et al., 1992), intracytoplasmic sperm injection (ICSI) has become a powerful tool for infertile couples — particular in cases of severe male infertility and low sperm counts. In ICSI, the 'best-looking' live spermatozoon is chosen for its motility, viability and gross morphology, using Hoffman contrast microscopy and a magnification of ×200 or ×400. Although the fertilization and clinical pregnancy rates associated with ICSI are high (Palermo et al., 2009), it has been shown that ejaculate characteristics (e.g. normal spermatozoa or mild or severe oligoasthenoteratozoospermia) (Loutradi et al., 2006) and the morphology of the individually selected spermatozoon may affect post-ICSI fertilization, implantation and pregnancy rates (De Vos et al., 2003). These results can be explained (at least in part) by the fact that, even though a spermatozoon's morphology is slightly correlated with its chromatin condensation or DNA integrity, the selection of normal spermatozoa during ICSI does not enable spermatozoa with nuclear defects to be excluded (Abu Hassan Abu et al., 2012; Avendaño et al., 2009).

Hence, over the last decade, some researchers have tried to improve sperm observation with higher-resolution microscopy techniques. Their objective has been to establish correlations between the morphology of a viable (and subsequently injectable) spermatozoon and its inherent quality (in terms of chromosomal content, degree of chromatin condensation and/or DNA integrity). The most studied of these novel techniques is motile sperm organelle morphology examination (MSOME), which uses differential interferential contrast microscopy and high magnification (>×6300), first described by Bartoov et al. (2001). This observation technique reportedly enables better assessment of a spermatozoon's morphology and the visualization of sperm head vacuoles. The latter structures are not visible (particularly when they are small) at a conventional ICSI-like magnification (using Hoffman contrast and a magnification of ×200—×400) (Bartoov et al., 2001). Nevertheless, since the introduction of IMSI, more attention has been given to the pre-ICSI detection of spermatozoa that contain vacuoles. Over the last decade, many researchers have evaluated IMSI (i.e. the MSOME-based selection of a spermatozoon and then its injection into the oocyte) and compared it with the gold-standard technique, ICSI. However, IMSI's superiority over ICSI (in terms of pregnancy or delivery rates) is still subject to debate. The only meta-analysis of this topic was performed 3 years ago (Setti et al., 2010). It included three studies and, by pooling all the IMSI results, did not take account of the specific indication. In fact, the studies in this field differ significantly in terms of: (i) their design (e.g. randomized versus non-randomized studies, or the comparison of IMSI results with previous ICSI results for the same couples versus other couples matched according to various criteria); (ii) the ICSI magnification used; (iii) the sprm morphology designated as 'normal' at an IMSI-like magnification; (iv) the sperm classification; and (v) the criteria used to assess the outcome (e.g. clinical pregnancy and delivery rates per couple, per transfer or per cycle).

Hence, the objective of the present literature review was to assess the outcomes for IMSI vs. ICSI and determine the clinical situations in which the use of this assisted reproduction technology is likely to be of greatest value.

Materials and methods

This work performed a systematic review of the relevant literature, according to the PRISMA guidelines (Moher et al., 2009). The PubMed database was searched for work published between 2001 and March 2013 with the following search terms: 'IMSI', 'MSOME' and 'high-magnification, sperm'. The publications' titles, abstracts and reference lists were viewed and only relevant publications (i.e. those reporting on IMSI outcomes in terms of blastocyst, pregnancy, delivery and/or live birth rates) in English were selected and included. This review examined, compared and discussed study methodologies and results, including patient characteristics, the magnifications used for IMSI and ICSI (when stated) and the pregnancy and/or delivery rates associated with IMSI and ICSI. The results were subdivided into currently accepted indications of IMSI (i.e. clinically relevant indications confirmed by several studies, including at least two randomized clinical trials with a large sample size) and potential indications (i.e. those requiring additional research).

Results and discussion

Literature retrieved

The PubMed search identified a total of 168 publications (58 using the term 'IMSI', 28 using the term 'MSOME' and 82 using the terms 'high-magnification, sperm') indexed between 2001 and March 2013. After viewing the publications' titles, abstracts and reference lists, 24 studies which directly compared IMSI and ICSI were retrieved. Following the exclusion of two publications not written in English, a total of 22 studies were included in this review.

Indication for IMSI

In most studies, ICSI was indicated because of the presence of at least one male factor for infertility (oligo- and/or astheno- and/or teratozoospermia) (see, for example, Table 1). The indication of ICSI was not specified in three studies and varied in one other study. The only confirmed indication of IMSI is recurrent implantation failure following ICSI.

Outcomes after IMSI

The outcomes of IMSI following ICSI failure are summarized in Table 1.

In two studies, IMSI was directly compared with ICSI in couples matched for the number of previous ICSI failures (Bartoov et al., 2003; Oliveira et al., 2011). Bartoov et al. studied a total of 100 couples with an mean (range) of 4.1 (2—8) previous ICSI failures. When compared with ICSI (performed at a magnification of ×200 or ×400, $n = 50$ couples), IMSI (with selection of normal spermatozoa with no more than one small vacuole occupying <4% of the sperm head area, $n = 50$ couples) yielded a significantly higher clinical pregnancy rate per couple (30% versus 66%, respectively,

Table 1 Studies comparing ICSI and IMSI outcomes.

Publication	*Indication for ICSI*	*Indication for IMSI*	*No. of couples*	*Randomized trial*	*Findings*			
					Outcome	*With IMSI (%)*	*With ICSI (%)*	*P-value*
Bartoov et al. (2003)	Male factor	Couples matched for the number of previous ICSI failures ($n \geq 2$)	100	No	CPR/couple	66	30	<0.01
					MR	9	33	<0.01
					DR/couple	60	20	<0.01
Oliveira et al. (2011)	—	Couples matched for the number of previous ICSI failures ($n \geq 2$)	200	No	CPR/cycle	26	19	NS
					MR	15	32	—
					LBR/cycle	21	12	NS
Hazout et al. (2006)	Male factor (n = 88) or not (n = 37)	Couples with previous ICSI failures ($n \geq 2$)	125	No	CPR/transfer	38	2	<0.001
					DR/transfer	34	0	<0.001
					LBR/transfer	18	0	<0.001
El Khattabi et al. (2013)	Male factor	Couples with previous ICSI failures ($n \geq 2$)	220	No	CPR/cycle	24	26	NS
					LBR/cycle	21	22	NS
Knez et al. (2011)	Male factor	Couples with previous ICSI failures (number not specified)	57	Yes	CPR/cycle	25	8	NS
Antinori et al. (2008)	Male factor	Couples with previous ICSI failures ($n \geq 2$)	139	Yes	CPR/couple	30	13	0.02
					MR	17	38	—
Klement et al. (2013)	Male factor	Couples with previous ICSI failures ($n \geq 1$)	449	Yes	CPR/cycle	56	38	0.002
					DR/cycle	28	18	0.04
De Vos et al. (2013)	Male factor	Unselected couples	340	No	CPR/transfer	34	37	NS
Balaban et al. (2011)	—	Unselected couples	168	Yes	CPR/cycle	54	44	NS
					LBR/cycle	44	38	NS

The study data confirm recurrent ICSI failure as the main indication of IMSI.
CPR = clinical pregnancy rate; DR = delivery rate; LBR = live birth rate; MR = mscarriage rate; — = not determined.

$P < 0.01$), a lower miscarriage rate (33% versus 9%, $P < 0.01$) and a higher delivery rate per couple (20% versus 60%, $P < 0.01$). Furthermore, IMSI yielded even higher clinical pregnancy and delivery rates per couple (50%, in both cases) in a group of 12 additional, unmatched couples with more than eight ICSI failures (although the technique was not compared directly with ICSI; Bartoov et al., 2003). Oliveira et al. studied 200 couples having undergone IMSI (with selection of normal spermatozoa with no more than one small vacuole occupying <4% of the sperm head area) and found that clinical pregnancy and live birth rates per cycle tended to be higher and miscarriage rates tended to be lower than those of the 100 couples having undergone ICSI (performed at a magnification of ×400), although these differences were not statistically significant (Oliveira et al., 2011). The comparison of these two studies suggest that sperm abnormalities that are not visible at ×200 might indeed be detected at magnification ×400. Hence, IMSI's superiority over ICSI at ×400 might be less obvious than IMSI's superiority over ICSI at ×200.

Hazout et al. (2006) compared outcomes for IMSI and ICSI (×200) in a total of 125 couples acting as their own controls. After at least two previous failed ICSI attempts, each couple underwent two further attempts: an additional round of ICSI (×200) and then IMSI (with selection of vacuole-free spermatozoa). When compared with the ICSI cycle, IMSI was associated with a significantly higher clinical pregnancy rate per transfer (2% versus 38%, respectively, $P < 0.001$) and a significantly lower miscarriage rate (data not reported). Furthermore, IMSI led to a significantly higher delivery rate per transfer (34% for IMSI and 0% for ICSI, $P < 0.001$) and a significantly higher live birth rate per embryo transferred (18% versus 0%, respectively, $P < 0.001$) than ICSI did (Hazout et al., 2006).

Very recently, a prospective but non-randomized study compared IMSI and ICSI outcomes in patients with more than two ICSI failures (El Khattabi et al., 2013). This was the only study to report that IMSI (with selection of the 'best available' spermatozoon, according to Vanderzwalmen et al., 2008) yielded much the same results (in terms of clinical

pregnancy and live birth rates per cycle) as ICSI performed at ×200 (24% versus 26% and 21% versus 22%, respectively). However, the fact that patients were not matched for the number of previous ICSI failures may have been a source of bias. The mean number of attempts for the IMSI patients (4.8) was indeed significantly greater than that for the ICSI patients (4.1; $P = 0.0001$).

Randomized studies (and particularly those with large sample sizes) provide the most robust evidence when comparing IMSI and ICSI outcomes. Knez et al. (2011) performed a randomized trial in patients with no blastocyst formation in previous ICSI failures. The researchers compared IMSI (with selection of the best spermatozoon, according to Cassuto et al. (2009), $n = 37$) and ICSI (performed at magnification of both ×200 and ×400, $n = 20$). There was a non-significant trend towards a higher number of cycles with at least one blastocyst in the IMSI group than in the ICSI group (50% versus 35%, respectively). Likewise, a non-significant trend towards a higher clinical pregnancy rate per cycle was achieved in the IMSI group, when compared with the ICSI group (25% versus 8%, respectively). Given that several factors (e.g. low oocyte quality) could be responsible for absence of blastocyst formation and that the study's sample size was small, it remains to be determined whether IMSI is indeed better than ICSI in this precise indication of no blastocyst formation.

Another randomized study (Antinori et al., 2008) of a larger number of couples ($n = 446$) compared 227 IMSI attempts (with selection of normal spermatozoa with no more than one small vacuole with a borderline diameter of 0.78 ± 0.18 μm) with 219 ICSI attempts (at an unspecified magnification). Overall, IMSI yielded a significantly higher clinical pregnancy rate per couple than ICSI (39% versus 27%, respectively; $P = 0.004$). For the 139 couples with at least two ICSI failures (**Table 1**), IMSI in 77 couples was associated with a 2-fold higher clinical pregnancy rate per couple than ICSI in 62 couples (30% versus 13%, respectively) and a 2-fold lower miscarriage rate (17% versus 38%). For couples with no previous ICSI failures ($n = 123$) or only one previous ICSI failure ($n = 184$), the clinical pregnancy rates per couple for IMSI and ICSI did not differ significantly (Antinori et al., 2008).

Very recently, it was suggested that IMSI may be of value after just one previous ICSI failure (Klement et al., 2013). In fact, this group led by Berkovitz performed a randomized study of a very large number (449) of couples with one previous ICSI failure. The clinical pregnancy and delivery rates per cycle were significantly higher for the 127 couples randomized to IMSI (with selection of normal spermatozoa with no more than one small vacuole occupying <4% of the sperm head area) than for the 322 couples randomized to further ICSI (at a magnification of ×200 or ×400): 56% versus 38% ($P = 0.002$) and 28% versus 18% ($P = 0.04$), respectively. A multivariate analysis prompted these researchers to state that the ICSI-to-IMSI switch after the initial failure was associated with a 3-fold greater chance of clinical pregnancy and delivery. Furthermore, the study results also showed that IMSI was no better than ICSI when used in the first round of treatment.

Other researchers have shown that IMSI is no more efficient than ICSI in unselected patients (i.e. regardless of the number of treatment attempts) (Balaban et al., 2011; De Vos et al., 2013). De Vos et al. (2013) recently analysed the outcomes of 350 attempts (including 125 IMSI cycles with the transfer of IMSI-only embryos and 139 ICSI cycles with the transfer of ICSI-only embryos) in a non-randomized study of 340 couples. The researchers reported that IMSI (with selection of vacuole-free spermatozoa, when available) yielded much the same results (in terms of clinical pregnancy rates per embryo transferred) as ICSI performed at a magnification of ×400 (34% versus 37%, respectively). However, most of the patients included in this study were undergoing their first ICSI/IMSI attempt (188/350, 54%) or second attempt (72/350, 21%). Hence, this study provided additional evidence for the lack of superiority of IMSI in patients with no previous ICSI failures. Similarly, Balaban et al. (2011) compared the outcomes of IMSI ($n = 87$) and ICSI ($n = 81$) in a randomized study of 168 unselected couples (i.e. regardless of any previous ICSI or IVF failures). Clinical pregnancy rates per cycle (54% versus 44%) and live birth rates per cycle (44% versus 38%) did not significantly differ when comparing the IMSI group (with selection of normal spermatozoa with no more than one small vacuole with a borderline diameter of 0.78 ± 0.18 μm) and the ICSI group (for which the magnification was not stated in the report).

In summary, the literature review results suggest that IMSI is only of value (in terms of higher clinical pregnancy and live birth rates) for patients with one or more previous ICSI failure and not for unselected patients or those undergoing their first treatment attempt. Given that (i) vacuoles were shown to be linked to chromatin condensation failure (Boitrelle et al., 2011; Boitrelle et al., 2013; Franco et al., 2012; Garolla et al., 2008; Perdrix et al., 2011), (ii) chromatin condensation failure is associated with recurrent abortions (Kazerooni et al., 2009; Talebi et al., 2012) and (iii) a growing body of evidence suggests that the degree of sperm chromatin condensation at the time of fertilization can influence early and late embryo development (Hammoud et al., 2011), the current work postulates that the higher pregnancy and delivery rates and lower miscarriage rates observed for IMSI after ICSI failure can be explained (at least in part) by the exclusion of spermatozoa containing sperm head vacuoles of nuclear origin.

Potential indications of IMSI

Teratozoospermia

Teratozoospermia may be an indication for IMSI. In all but one of the studies reviewed below, ICSI and IMSI were indicated because of the presence of at least one male factor for infertility (oligo- and/or astheno- and/or teratozoospermia). The article by Berkovitz et al. (2006) did not specify an indication.

It has already been shown that individual spermatozoa differ in their ability to produce an embryo capable of implanting. Indeed, the use of morphometrically normal spermatozoa with no vacuoles or less than two small vacuoles has been associated with significantly higher blastocyst rates than all other types of spermatozoa (i.e. those with more than two small vacuoles, those with one large vacuole and those with morphometric abnormalities) (Knez et al., 2012; Vanderzwalmen et al., 2008). In contrast, one study has reported lower blastocyst rates when vacuole-free spermatozoa were used for injection (relative to spermatozoa with vacuoles)

(Tanaka et al., 2012); however, the sample size was small and the study population was not homogeneous because it included both patients with azoospermia and patients with normal sperm characteristics. Furthermore, concerning the ability of individual spermatozoa to lead to a pregnancy, the shape of the sperm head and the presence of vacuoles were reported as being significantly and positively correlated with the chance of achieving a pregnancy with IMSI ($r = 0.38$; $P \leq 0.01$; Bartoov et al., 2002). Berkovitz et al. (2006) reported on IMSI in 80 patients: when compared with spermatozoa with vacuoles or an abnormal morphology (so-called 'second-choice' spermatozoa), normal, vacuole-free spermatozoa yielded significantly higher clinical pregnancy and delivery rates per cycle (58% versus 26% and 53% versus 17%, respectively, both $P \leq 0.01$) and significantly lower miscarriage rates (10% versus 33%, respectively; $P = 0.02$) (Berkovitz et al., 2006). Hence, the morphology of individually selected spermatozoa seems to have an impact on pregnancy and delivery rates.

This is why some researchers have tried to determine a threshold for the proportion of normal spermatozoa below which ICSI might be inefficient or, conversely, IMSI might be of value. Two studies have evaluated ICSI results as a function of the proportion of normal spermatozoa in the ejaculate, as assessed by MSOME (Bartoov et al., 2002; Falagario et al., 2012). It was shown that normalcy of the sperm nucleus (i.e. a normal shape and with less than one small vacuole occupying <4% of the sperm head area) was predictive of the clinical pregnancy rate after ICSI (Bartoov et al., 2002). Even though <20% of normal spermatozoa were found in the ejaculate with MSOME, no pregnancies were obtained after ICSI performed at a magnification of ×200–×400 (Bartoov et al., 2002). Another study contributed additional data on this matter by reporting that the lower the proportion of normal spermatozoa in the ejaculate (as assessed by MSOME, with a threshold of 20%), the higher the risk of choosing a vacuolated spermatozoon with conventional ICSI and the lower the clinical pregnancy rate with conventional ICSI (Falagario et al., 2012). Hence, the proportion of normal spermatozoa (as assessed by MSOME) and the quality of the ICSI outcomes seem to decrease in parallel. Similarly, a group of researchers compared IMSI outcomes as function of the proportion of normal spermatozoa (as assessed by MSOME) in the ejaculate (Berkovitz et al., 2005). They reported that IMSI in which normal, vacuole-free spermatozoa were available for injection ($n = 126$ IMSI cycles) yielded a significantly higher clinical pregnancy rate per transfer and a significantly lower miscarriage rate relative to IMSI ($n = 38$ cycles) in which no normal spermatozoa were available (respectively 53% versus 18%, $P \leq 0.01$; 10% versus 57%; $P = 0.02$) (Berkovitz et al., 2005). This finding suggested that even in the absence of normal spermatozoa (according to MSOME), pregnancy rates were low but not null with IMSI. Hence, IMSI might be preferable to ICSI when few normal spermatozoa (as assessed by MSOME) are present in the ejaculate. Very recently, a prospective but non-randomized study (El Khattabi et al., 2013) compared IMSI and ICSI results in patients with teratozoospermia (defined as <10% of normal spermatozoa in a spermocytogram, according to David's criteria (Auger et al., 2001)). In this study, IMSI (with selection of the 'best available' spermatozoon, according to Vanderzwalmen's criteria (Vanderzwalmen et al., 2008)) yielded higher clinical pregnancy and live birth rates per cycle than ICSI performed at a magnification of ×200 (46% versus 26%, $P = 0.001$ and 38% versus 20%, $P = 0.002$, respectively). However, randomized ICSI versus IMSI studies constitute the only way of robustly testing the value of IMSI in cases of teratozoospermia.

The only study of this type to date was performed recently in patients with isolated teratozoospermia (defined as <14% of normal spermatozoa in a spermocytogram, according to Kruger's strict criteria; Knez et al., 2012). In this randomized study, 52 couples underwent IMSI (with selection of the 'best available' spermatozoon, according to Vanderzwalmen's criteria) and 70 underwent ICSI (performed at a magnification of ×200–×400). The clinical pregnancy rates per couple were significantly higher for IMSI than for ICSI (48% and 24%, respectively; $P < 0.05$). However, Knez et al. did not state threshold values for the number or proportion of normal spermatozoa (as assessed by MSOME) below which IMSI (rather than ICSI) could be indicated because the couples were not matched by the degree of teratozoospermia (Knez et al., 2012).

In contrast, one can legitimately question whether IMSI is indicated in some types of teratozoospermia. It appears that IMSI was ineffective (or no more efficient than ICSI, at least) in patients with a high proportion of spermatozoa with enlarged heads (Chelli et al., 2010), since normal spermatozoa selected at both ICSI-like and IMSI-like magnifications were potentially aneuploid. In cases of globozoospermia, however, IMSI might enable the selection of spermatozoa with a small acrosomal bud. Indeed, IMSI enabled a successful pregnancy for a couple in which the male displayed almost total globozoospermia (99% of the spermatozoa were round-headed), in the absence of assisted oocyte activation (Sermondade et al., 2011).

In summary, IMSI might be indicated in some cases of teratozoospermia. However, given that only one randomized study observed higher clinical pregnancy rates for IMSI than for ICSI in patients with teratozoospermia and the threshold for the number of morphometrically normal spermatozoa (as assessed by MSOME) below which IMSI might produce higher clinical pregnancy and delivery rates than ICSI remains to be determined, further studies of the potential value of IMSI in patients with teratozoospermia are required.

IMSI and spermatozoa with nuclear abnormalities

The use of IMSI might help to avoid the selection of spermatozoa with nuclear abnormalities such as chromatin condensation failure, DNA fragmentation and an abnormal chromosomal content.

First, given that the nuclear origin of sperm head vacuoles has been linked to chromatin condensation failure, a high proportion of non-condensed chromatin could be considered as an indication for IMSI. No data are available but this question deserves to be evaluated in large-scale, randomized trials.

A second potential indication of interest is sperm DNA fragmentation. Indeed, it has been shown that spermatozoa judged to be normal at ICSI-like magnifications can present DNA fragmentation and that normal vacuole-free spermatozoa selected at an IMSI-like magnification are less DNA fragmented than normal spermatozoa selected at an

ICSI-like magnification (Hammoud et al., 2013). However, only one study has compared IMSI and ICSI outcomes in patients with high levels of sperm DNA fragmentation (Hazout et al., 2006), in which 72 couples with two or more previous ICSI failures were subdivided according to the proportion of spermatozoa with DNA fragmentation in the male's whole semen: normal (i.e. <30% of spermatozoa with DNA fragmentation, $n = 51$), moderately elevated (30–40%, $n = 11$) and greatly elevated (>40%, $n = 10$). Overall, IMSI yielded significantly higher clinical pregnancy, delivery and birth rates per transfer than ICSI (performed at a magnification of ×200) did, with values of 38% versus 2%, 34% versus 0% and 18% versus 0%, respectively ($P < 0.001$ for all comparisons). For patients with normal proportions of DNA-fragmented spermatozoa, the birth rate was 19% for IMSI and 0% for ICSI ($P < 0.001$). The superiority of IMSI over ICSI (in terms of birth rates) was particularly obvious in the group with the highest percentage of DNA-fragmented spermatozoa (29% versus 0%, respectively; $P < 0.01$), although the small sample size reduced the statistical significance (Hazout et al., 2006). Given that the sample size was small and the study was not randomized, it remains to be seen whether IMSI is indicated in cases of sperm DNA fragmentation. This potential indication deserves to be evaluated in large-scale randomized trials.

Thirdly, sperm aneuploidy may be considered. Although two studies have reported that spermatozoa with large vacuoles are more likely to be aneuploid than normal, vacuole-free spermatozoa (Garolla et al., 2008) or spermatozoa from whole semen (Perdrix et al., 2011), IMSI was found to be no more efficient than ICSI for selecting euploid spermatozoa in patients with a high proportion of aneuploid spermatozoa (e.g. patients with a high proportion of spermatozoa with enlarged heads (Chelli et al., 2010) or translocations (Cassuto et al., 2011; Chelli et al., 2013)). Hence, it has not been proved that IMSI can be used to efficiently select euploid spermatozoa. Indeed, one can even consider that the opposite is true (i.e. a demonstrated lack of efficiency).

IMSI for older women

Interestingly, only one research group has evaluated IMSI in older women. In a randomized study of patients with a mean age of 37, preimplantation genetic diagnosis showed that ICSI ($n = 60$) was associated with significantly higher sex chromosome aneuploidy in the embryo and a significantly greater proportion of chaotic embryos (i.e. with two or more chromosomal number abnormalities) relative to IMSI ($n = 60$). The researchers postulated that, in older women, oocytes were less able to repair the injected spermatozoon's DNA and hence that use of IMSI to select spermatozoa with fewer nuclear abnormalities could be of value for aged oocytes and older women (Figueira et al., 2011). This indication also deserves to be evaluated in large-scale, randomized trials.

IMSI for everyone

Some authors go as far as to suggest that IMSI can be used for all couples in assisted reproduction programmes. They argue that, relative to ICSI, IMSI increases the likelihood of obtaining a healthy, normal child (Berkovitz et al., 2007). In the latter study, children ($n = 176$) born after ICSI had a significantly greater risk of major congenital malformations than those born after IMSI ($n = 181$; 8% versus 3%, respectively; $P = 0.02$). However, the value of 8% is the highest post-ICSI malformation rate ever reported and casts doubt on the reliability of the study data (for a meta-analysis, see Wen et al., 2012). Hence, one cannot conclude as to the potential value of IMSI for reducing congenital malformations; only randomized studies in a large number of patients are capable of providing robust information.

Conclusion

A decade after the introduction of IMSI, this technique continues to divide assisted reproduction professionals. There are few confirmed indications of IMSI, partly because few randomized, head-to-head studies have been performed. According to this systematic literature review, the only currently and consistently acknowledged indication of IMSI is recurrent implantation failure following ICSI. All other potential indications of IMSI must be further assessed.

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