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Relationship between oocyte abnormal morphology and intracytoplasmic sperm injection outcomes: a meta-analysis

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ABSTRACT

The aim of this study was to perform a meta-analysis of the potential effects of oocyte morphological abnormalities on ICSI outcomes. Relevant original papers reporting on the relation between oocyte morphology and ICSI outcomes were identified by searching MEDLINE, EMBASE and the Cochrane Library. The main outcome measures were fertilisation rate and embryo quality. A meta-analysis was performed and Mantel–Haenszel pooled odd ratios (ORs) with 95% confidence intervals (CIs) were calculated to express the relation between the oocyte morphology and the ICSI outcomes. A total of 14 studies reporting 3688 ICSI cycles were included. Our meta-analysis demonstrates that the probability of an oocyte becoming fertilised is significantly reduced by the presence of large IPB (OR: 0.29, CI: 0.09–0.90), large PVS (OR: 0.86, CI: 0.74–0.99), refractile bodies (OR: 0.66, CI: 0.51–0.84) or vacuoles (OR: 0.59, CI: 0.42–0.83). No other investigated morphological abnormalities demonstrated significant relationships with ICSI outcomes. Our data demonstrate that the presence of large IPB, large PVS, refractile bodies or vacuoles is associated with decreased oocyte fertilisation. Our findings might be of importance for selecting embryos for replacement because the effects of oocyte abnormalities on implantation and pregnancy rates remain unclear.

1. Introduction

The acquisition of oocyte competence relies on a complex cascade of events that occurs during follicular development. In the course of acquiring these competencies, cytoplasmic changes occur that include mRNA transcription, protein translation, post-translational modification of proteins and ultrastructural changes [1,2]. Successful completion of these events is independent of nuclear maturation and is collectively referred to as cytoplasmic maturation [3].

As an oocyte grows and matures, it acquires the ability to resume and complete meiosis [4], successfully undergo the fertilisation process, initiate and sustain embryonic development [1–3]. An oocyte that has not completed cytoplasmic maturation is of poor quality, and thus unable to successfully complete normal developmental processes. However, the mechanisms that impair oocyte developmental competence are still unclear [3].

Application of ovarian stimulation in human reproduction further complicates the situation. In contrast to the in vivo process, where oocyte maturation occurs as the result of a natural selection procedure [5], in stimulated cycles, pharmacologic doses of gonadotrophins create a supraphysiologic hormonal environment that induces the growth of a cohort of follicles, which, under natural conditions, would become atretic and regress [6], allowing successful maturation of oocytes with compromised quality [7].

Nuclear maturity alone is neither sufficient to determine the competence of an oocyte, nor to ensure that the meiotic apparatus of the oocyte has progressed correctly to metaphase II (MII) stage [8]. A deficiency in cytoplasmic maturation could compromise all processes that prepare the oocyte for activation and adequate fertilisation. Moreover, the morphological appearance of the oocyte may indicate the developmental potential of the subsequent embryo [5].

With the advent of intracytoplasmic sperm injection (ICSI), which requires the denuding of the oocyte from the cumulus-corona cells, a wide range of information regarding oocyte morphology has emerged and permits the oocyte to be observed immediately before sperm injection using an inverted microscope. It is generally accepted that good-quality human MII oocytes should have a clear, moderately granular cytoplasm that does not contain inclusions, a small perivitelline space (PVS) containing a single unfragmented IPB and a round, clear, colourless zona

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pellucida (ZP) [5,9,10]. Nevertheless, more than half of all collected oocytes show at least one morphological abnormality [11,12].

Morphological abnormalities of oocytes are most commonly classified as either intracytoplasmic features (increased cytoplasmic granularity and presence of cytoplasmic inclusions) or extracytoplasmic features (large PVS, PVS granularity, and fragmented or irregular IPB) [6].

Because the pre-selection of oocytes with the highest developmental potential, based on morphological criteria, is of obvious interest for improving the efficiency of assisted reproduction technology, numerous studies have reported the presence or absence of relationship between oocyte morphological abnormalities and ICSI outcomes [5,6,8,11,13–23]. Nevertheless, to date, the influence of all these oocyte features on the fertilisation rate (FR), top quality embryo rate (EQR), pregnancy rate (PR), and implantation rate (IR) is still controversial when using ICSI.

Meta-analysis provides an overall consensus from studies, resulting in a more precise estimate than any of the individual articles. The aim of this study was to perform the first meta-analysis of published data to evaluate the potential effects of oocyte morphological abnormalities on ICSI outcomes.

2. Materials and methods

2.1. Literature search

A computerised search in MEDLINE, EMBASE and the Cochrane Library (from inception of each database until June 2010) was performed to identify articles reporting on the relation between oocyte morphology and ICSI outcomes. Keywords used were oocyte and dysmorphism; oocyte morphology and ICSI. The search was restricted for articles written in English. References detected with the related articles function in Pubmed were also checked to identify cited articles not captured by electronic searches. The reference lists of eligible primary studies were examined for identification of additional articles.

2.2. Study selection and data extraction

To ensure independence of effects, studies could contribute more than one effect only when data from independent samples were analysed separately (if the effect of an individual oocyte morphological abnormality on ICSI outcome was investigated). Assessment of denuded oocyte morphology had to be obtained by an embryologist under an inverted microscope. Studies dealing with animal oocytes, *in vitro* matured or cryopreserved oocytes and focusing on a specific clinical situation (i.e., polycystic ovary syndrome) were excluded from the subsequent analysis. No strict selection according to the experimental designs was applied. Because a meta-analysis on the effects of meiotic spindle visualisation on ICSI outcomes was recently published [24], the articles dealing exclusively with this morphological evaluation were excluded from the study. The primary outcomes were fertilisation and embryo quality.

Studies were selected in a two-stage process (illustrated in Fig. 1). At the first screening, the titles and abstracts from the electronic searches were scrutinized by two reviewers independently (A.S. and R.F.). Studies with lack of any relevance were excluded and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Second, final inclusion or exclusion decisions were made on examination of full manuscripts by both reviewers.

Two independent investigators (A.S. and R.F.) extracted the data from all eligible trials. Discrepancies were resolved by the involvement of another investigator (D.B.). From each eligible trial we recorded for both arms the following data: demographic (authors, type of study, country of origin, patients' mean age at enrollment and period of enrollment), procedural (number of patients included, inclusion and exclusion criteria for patients populations and type of COH protocol) and outcome data (fertilisation, embryo quality, implantation, pregnancy and miscarriage rates). The Newcastle-Ottawa Quality Assessment Scales for observational studies [25] were implemented. This instrument

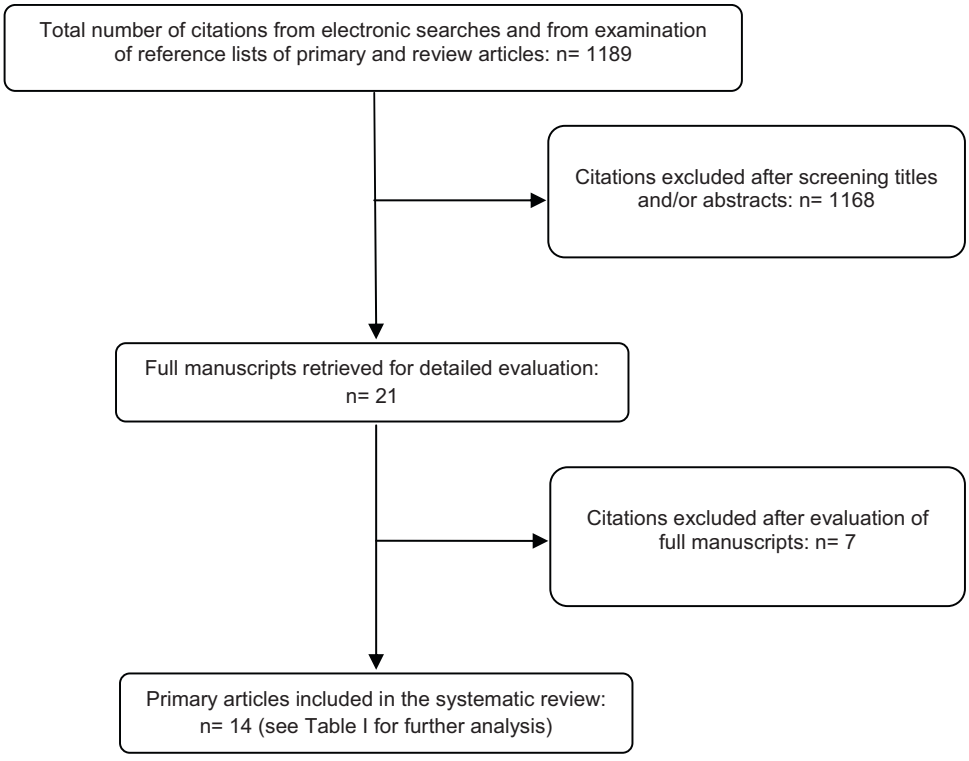

Fig. 1. Study selection process for systematic review.

Table 1
Quality and characteristics of the studies included in the meta-analysis.

Trial (year)	Design	Methods	ICSI cycles (*n*)	Female age	Indication	MII oocytes (*n*)	Oocyte morphological evaluation									Newcastle-Ottawa scale QAC, S/C, O
							IPB	PVS	PVSgran	ZP	Shape	Ccolor	Cgran	Rbody	Vac	
De Sutter et al. (1996)	R	The FR and embryo score were correlated with oocyte morphology.	56	–	Severe sperm deficiencies or at least one previous IVF failure	528		*		*	*			*	*	2,1,3
Serhal et al. (1997)	R	The cytoplasmic morphology of the oocytes were correlated with the FR, EQ on day 2, IR and PR.	106	<37	Male factor	837							*			4,1,2
Xia (1997)	R	FR and EQ on day 2 were correlated to oocyte dysmorphisms.	65	≤40	Low fertilisation or <500.000 spermatozoa in the ejaculate	903	*	*								2,1,3
Balaban et al. (1998)	R	FR and EQ on day 2 were correlated to oocyte dysmorphisms. PR, IR and MR were compared in cycles with all embryos derived from morphologically normal oocytes and abnormal oocytes.	654	–	Male factor	5903		*		*	*	*	*	*		3,1,3
Hassan-Ali et al. (1998)	R	ICSI outcomes were compared between two groups according to PVSgran. Outcomes of oocytes with granularity and without granularity were also compared.	206	Group A: 32 ± 0.4 Group B: 31.7 ± 0.6	Male factor	2063			*		*					2,1,2
Ebner et al. (2000)	R	IPB morphology was assessed and correlated to the FR and EQ on day 2.	70	≤40	Male factor or at least 2 previous IVF failures	544	*			*		*		*		2,1,3
Verlinsky et al. (2003)	P	IPB morphology was assessed and correlated to the FR, EQ on day 3, 5 and 6, IR and PR.	91	37 ± 3.6	Different indication	831	*									2,1,2
Ciotti et al. (2004)	R	IPB morphology was assessed and classified as intact or fragmented. The FR and EQ on day 2, IR and PR were evaluated.	167	35.4 ± 3.9	Male factor or previous IVF failure	596	*									3,1,1
De Santis et al. (2005)	P	IPB morphology was assessed and classified as intact and normal size, fragmented, rough or enlarged. The FR and EQ were evaluated on day 2.	382	35.0 ± 4.9	Male factor or previous fertilisation failure	873	*									3,1,2
Ebner et al. (2005)	P	Size and number of vacuoles were correlated to FR, blastocyst formation rate and quality.	165	32.7 ± 4.6	Male factor and/or previous IVF failure	1198									*	4,1,3
Chamayou et al. (2006)	R	Oocyte dysmorphisms were correlated to EQ on day 2, IR and PR.	404	34.6 ± 5.4	Male factor and/or previous IVF failure and/or female factor	967	*	*	*				*			3,1,2
Fancsovits et al. (2006)	R	IPB morphology was assessed and the FR and EQ were evaluated on day 2.	522	–	–	3387	*									2,0,3
Fancsovits et al. (2006)	R	IPB morphology was assessed and the FR and EQ were evaluated on day 2.	522	–	–	3387	*									2,0,3
Ten et al. (2007)	R	The predictive value of oocyte dysmorphisms on FR and EQ was evaluated in 126 donor women.	160	<35	Ovodonation and male factor	1622	*	*	*		*	*			*	4,1,3
Navarro et al. (2009)	R	IPB morphology was assessed and classified as intact and normal size, fragmented or enlarged. The FR, cleavage and EQ were evaluated on day 2.	582	<40	Male factor	3177	*									2,1,3

Design: R, retrospective study; P, prospective study. Outcome: FR, fertilisation rate; EQR, embryo quality rate; IR, implantation rate; PR, pregnancy rate. Oocyte morphological evaluation: IPB, A1:Q18 first polar body morphology; PVS, perivitelline space size; PVSgran, perivitelline space granularity; ZP, dark zona pellucida; shape, oocyte shape; Cgran, cytoplasmic granularity; Rbody, refractile body; Vac, vacuole; QAC, quality assessment criteria; S/C, selection/comparability; O, outcome; *, investigated morphological feature. –, data not provided.

assesses the quality of nonrandomized studies in 3 broad categories (patient selection [4 criteria], comparability of study groups [1 criterion], and assessment of the outcome [3 criteria]). Following quality assessment standards of previous meta-analyses, 20 studies in our meta-analysis that met 5 or more of the Newcastle-Ottawa Scale criteria were considered to be of higher quality.

2.3. Statistical analysis

From each study, outcome data were extracted in 2×2 tables by the two reviewers (A.S. and R.S.). The measure of heterogeneity (non-combinability) was evaluated by I^2. For a non-significant I^2 result a fixed model was used. For a significant I^2 result, a random model (DerSimonian and Laird [44]) was used. The results were pulled using Mantel–Haenszel statistic model and are expressed as ORs with 95% confidence intervals (CIs). The meta-analysis was conducted using the RevMan 5 Software (Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Literature identification and study characteristics

The process of literature identification and selection is summarised in Fig. 1. A total of 1189 studies were initially retrieved from the literature. After the first screening, a total of 21 published studies, which analysed the relationship between the oocyte morphological abnormalities and ICSI outcomes were considered for inclusion [5,6,8,11,13–23,26–31]. After the second screening, out of the 21 studies, 14 fulfilled our predetermined criteria [8,11,13–16,19–21,26–30]. The seven remaining studies were excluded due to a non-extractable 2×2 table or due to a particular oocyte evaluation method. The included studies and their characteristics, as well as the results for the Newcastle-Ottawa quality assessment scales are listed in Table 1. Investigated structures included the following: the shape of the IPB, the size and granularity of the PVS, the colour of the ZP, the shape of the oocyte, the cytoplasmic colour, granularity, and inclusions (refractile bodies and vacuoles). The effects of oocyte morphological abnormalities on implantation/pregnancy rates were investigated in three/two studies. These comparisons would be applicable in the context of single embryo transfer, however, this was not the case of any of the studies and these comparisons were not included in this meta-analysis.

3.2. Data on ICSI outcomes

The influence of oocyte morphological abnormalities on fertilisation rate and embryo quality is shown in Table 2. Forest plots are shown in Fig. 2.

4. Discussion

As an attempt to improve the results of ICSI cycles, it is important to identify and utilise non-invasive parameters able to predict oocyte quality. Considering the vital role played by the oocyte in the developmental process, selection criteria involving the stages preceding fertilisation would be extremely useful in selecting embryos for transfer. Nonetheless, previous reports are conflicting regarding the effects of oocyte morphological abnormalities on FR and EQR.

A strength of systematic reviews is the improved precision of the summary OR estimates compared with the individual studies. The meta-analytical approach is used as a precise investigation for those studies that could fit into the specific criteria. This is the first meta-analysis that draws together the reports of the ICSI cycles outcomes, addressing the question of whether there exists a relationship between oocyte morphological abnormalities and FR and EQR. Out of twenty-one relevant studies identified in the current literature, 14 studies met the eligibility criteria and were identified as suitable for this meta-analysis.

Our meta-analysis demonstrates that the probability of an oocyte becoming fertilised is significantly reduced by the presence of a large IPB, large PVS, refractile bodies or vacuoles.

Balaban and Urman [13] summarized the data in the literature that studied the effect of oocyte morphology on *in vitro* fertilisation (IVF). The authors suggested that the extracytoplasmic dysmorphisms should be considered only a phenotypic deviation resulting from the heterogeneity of the oocytes retrieved and the severe cytoplasmic dysmorphisms, such as SER, centrally severe granulation and excessive vacuolisation, should be considered as abnormal and taken into consideration for the selection of a viable oocyte.

Rienzi et al. [32] published a systematic review of the literature regarding the predictive value of oocyte morphology in IVF. The authors analysed 50 papers published in the past 15 years and concluded that their analysis has produced contradicting results, and did not entirely support the average opinion about the features of 'good' and 'bad' quality and respective developmental competence. Moreover, the study underlined the importance of more intensive research to reach a consensus and exploit fully the predictive potential of morphological examination.

In 2010, the alpha scientists in reproductive medicine and ESHRE special interest group of embryology convened a workshop addressing the morphological assessment of embryos. Recently, the proceedings of this expert meeting as well as the consensus points developed have been published [33]. It was the consensus opinion that the optimal oocyte morphology is that of a spherical structure enclosed by a uniform zona pellucida, with a uniform translucent cytoplasm free of inclusions and a size-appropriate

Table 2
Influence of oocyte morphological abnormalities on fertilisation rate and embryo quality.

Morphological abnormality	Fertilisation rate		Embryo quality	
	OR (CI)	Studies (*n*)	OR (CI)	Studies (*n*)
Fragmented IPB	1.00 (0.77–1.29)	7	0.74 (0.50–1.10)	8
Large IPB	0.29 (0.09–0.90)	4	0.42 (0.16–1.11)	5
Rough IPB surface	0.98 (0.84–1.15)	4	0.81 (0.47–1.40)	5
Large PVS	0.86 (0.74–0.99)	4	0.99 (0.58–1.70)	4
PVS granularity	1.03 (0.85–1.26)	2	1.15 (0.72–1.84)	3
Colour of the ZP	0.94 (0.77–1.13)	3	1.17 (0.93–1.47)	2
Shape of the oocyte	0.99 (0.83–1.17)	4	1.02 (0.83–1.25)	3
Cytoplasmic colour	0.92 (0.76–1.10)	3	0.64 (0.25–1.62)	3
Cytoplasmic granularity	0.89 (0.69–1.15)	2	1.15 (0.56–2.36)	3
Refractile bodies	0.66 (0.51–0.84)	3	1.06 (0.74–1.51)	2
Vacuoles	0.59 (0.42–0.83)	3	*	*

OR, odds ratio; CI, confidence interval; IPB, first polar body; PVS, perivitelline space; ZP, zona pellucida; *, not evaluated.

Figure 2.1 Effect of large IPB on fertilization rate

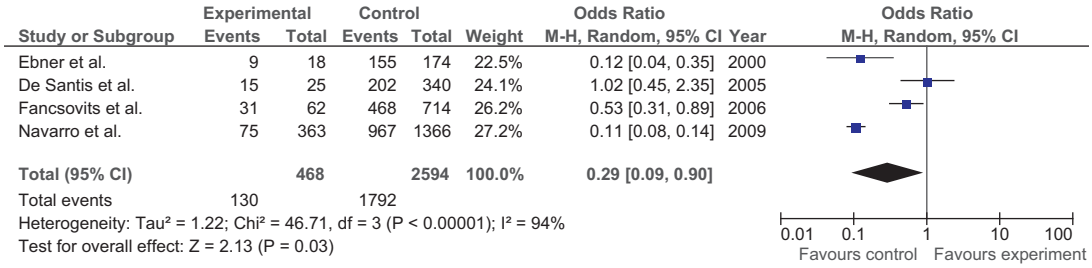

Figure 2.2 Effect of large PVS on fertilization rate

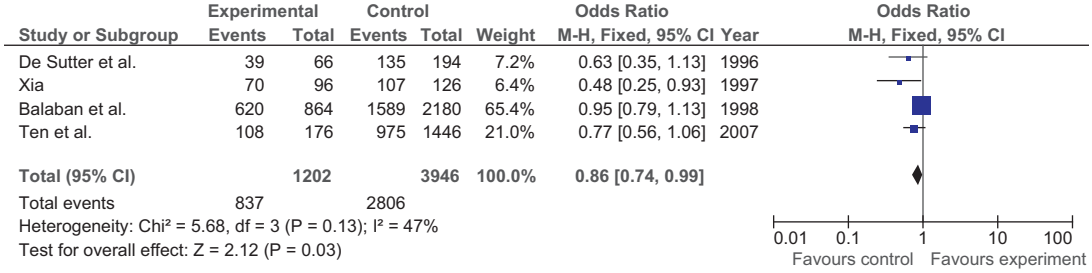

Figure 2.3 Effect of refractile bodies on fertilization rate

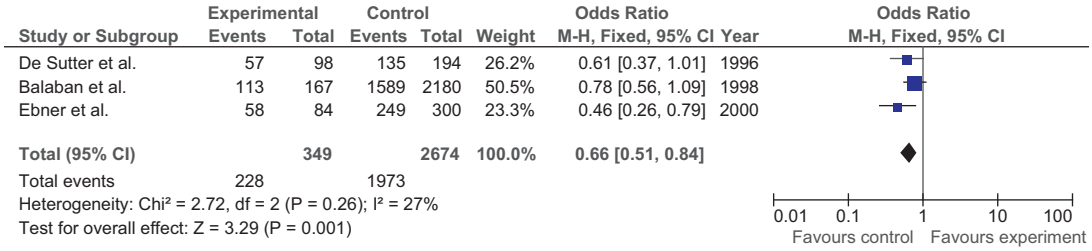

Figure 2.4 Effect of vacuoles on fertilization rate

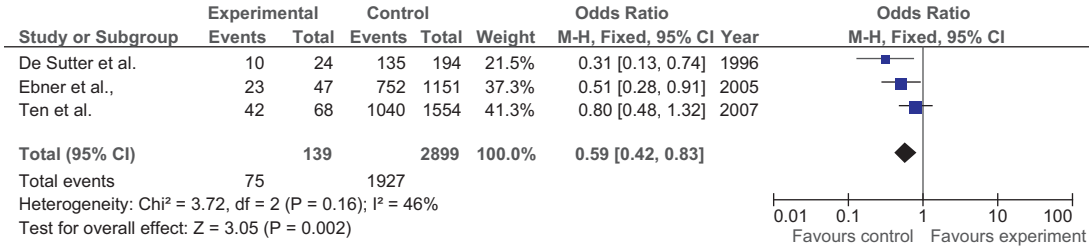

Fig. 2. Meta-analysis of the effects of oocyte morphological abnormalities on ICSI outcomes. Results are expressed as odds ratios (ORs) with 95% of confidence intervals (CIs). Individual studies are displayed with a black square. The line through the squares indicates the 95% CI. When the CI crosses the vertical line with OR = 1, there is no significant difference between the groups. The diamond in the last row of the graph illustrates the overall result of the meta-analysis. When the diamond does not cross the vertical line, the difference between the groups is considered as statistically significant. Fixed and random models assume homogeneous and heterogeneous studies, respectively.

polar body. It was further agreed that a note of both the perivitelline space and the size of the polar body should only be made if they are exceptionally large. Moreover, the observation of large vacuoles (>14 μm in diameter) should be noted. It was strongly recommended that oocytes presenting SER disks should not be inseminated.

Our result regarding the negative influence of a large IPB on fertilisation is in accordance with previous findings. Rienzi et al. [5] reported that abnormalities in the IPB significantly reduced by half the chance of oocyte fertilisation. It has been proposed that the extrusion of a large IPB is due to the dislocation of the meiotic spindle [5] and is associated with an increased rate of abnormal fertilisation [10]. Additionally, other studies have associated the IPB morphology with improved embryo quality [27], probability of development to a blastocyst [27], higher implantation [27,31] and pregnancy rates [31]. Nevertheless, this meta-analysis showed that once fertilised, these oocytes did not show compromised development potential *in vitro*.

Our meta-analysis also demonstrated that the presence of a large PVS significantly reduces the chance of oocyte fertilisation. This finding is in accordance with Rienzi et al. [5], who observed a significant decreased fertilisation in the presence of this morphological abnormality. Similarly, Figueira et al. [6] reported that the fertilisation rate was significantly affected by a large PVS. It has

been suggested that the presence of a large perivitelline space is associated with overmaturity of the oocyte.

Moreover, our study observed a significant reduction in the probability of fertilisation when oocytes presenting inclusions, such as vacuoles and refractile bodies, are injected. Our results regarding the negative influence of inclusions, such as vacuoles and refractile bodies, on fertilisation are in accordance with previous published papers [5,6,11,12,21].

It has been proposed that vacuoles arise either spontaneously or by fusion of vesicles derived from the smooth endoplasmic reticulum and/or golgi apparatus [26]. How vacuolisation affects fertilisation and pronuclear formation is still unclear. It has been suggested that the presence of intracytoplasmic vacuoles is associated with severe oocyte degeneration, displacement of the MII spindle from its polar position [9], abnormal cytokinesis pattern [9,34], compromised embryo development [13] and impaired blastocyst formation [26].

Nevertheless, previous studies observed similar fertilisation rates with the injection of "ideal" oocytes and those displaying vacuoles [19,35]; however, in one of them, no pregnancy was achieved when an embryo derived from a vacuolated oocyte was transferred [19]. Nevertheless, Rienzi et al. [32] did not find consistent evidence for that the presence of vacuoles affects pregnancy rate.

It has also been postulated that larger vacuoles are much more damaging to the oocyte than a small one. Ebner et al. [26] found a significant correlation between vacuole diameter and fertilisation, since no fertilisation was achieved in the presence of a vacuole diameter >14 μm. Accordingly, in a case report, Wallbutton and Kasraie [36] concluded that cytoplasmic macro vacuoles (25 μm) appear to distort oocyte cytoskeletal structure to an extent that physiological processes involved in fertilisation and embryogenesis, such as sperm–oocyte signaling, sperm binding, meiotic resumption and embryonic cleavage, are impaired.

Other studies did not evaluate vacuolisation, refractile bodies, and aggregates of smooth endoplasmic reticulum (SER) as individual features [11,19,21,22,37,38]. These features were characterised as cytoplasmic inclusions, a fact that could have influenced the results. Nevertheless, refractile bodies have been associated with fertilisation failure [11], and SER with lower chances of successful pregnancy [18].

The presence of both vacuoles and oocyte inclusions have been associated with lower fertilisation and clinical pregnancy rate clinical pregnancy rates [22], poor embryo development and higher aneuploidy rates [38]. Indeed, a higher rate of aneuploidy has been found in dysmorphic oocytes as compared to morphologically normal ones [17,39,40].

It is important to note that morphology of the meiotic spindle was not included in this study because a satisfactory meta-analysis on this topic has recently been published [24]. According to the study, the results showed statistically significant higher fertilisation rate, percentage of pronuclear stage embryos with good morphology, cleavage rate, percentage of day-3 top quality embryos, and percentage of embryos that reached the blastocyst stage, when the meiotic spindle was viewed than when it was not. However, the clinical pregnancy or implantation rates were not significantly different.

A weakness of this meta-analysis could be the fact that the studies investigating the association of oocyte morphology and ICSI outcomes were frequently retrospectively. We could have tried to minimize the heterogeneity by limiting the meta-analysis to a small more homogeneous group of studies. However, this limits the scope of the meta-analysis and essentially throws away useful information [41]. Moreover, it has been suggested that heterogeneity improves the generalizability of the results of the meta-analysis [42,43]. Therefore, it was decided to maintain all the included studies and use, whenever appropriate, the random effect model developed by DerSimonian and Laird [44], which incorporates the heterogeneity in the analysis of the overall result.

Based on our meta-analysis, we can conclude that the presence of a large IPB, large PVS, refractile bodies or vacuoles significantly reduces the chance of an oocyte becoming fertilised. It is important to emphasise that, because the studies rarely addressed the relationship between oocyte morphology and implantation and/or pregnancy rates, our findings might be of importance in selecting embryos for replacement because the effects of oocyte abnormalities on those outcomes remain unclear. Additionally, our results are relevant in countries where there is a legal limit on the number of oocytes that can be fertilised. Further prospective studies will be helpful in understanding the importance of oocyte morphological abnormalities on embryo quality, pregnancy and implantation.

Condensation

Our meta-analysis demonstrates that the probability of an oocyte becoming fertilised is significantly reduced by the presence of intracytoplasmic inclusions and extracytoplasmic dysmorphisms.

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