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REVIEW

FERTILITY & REPRODUCTION

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The Timing of Intracytoplasmic Sperm Injection Relative to Oocyte Retrieval: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: It is currently inconclusive whether different intracytoplasmic sperm injection (ICSI) timings post oocyte retrieval (POR) lead to altered chance of clinical pregnancy and live birth following *in vitro* fertilization (IVF) treatment. This study, therefore, aimed to synthesize literature-based evidence for better clinical guidance regarding ICSI practice.

Methods: A systematic review and meta-analysis were performed according to PRISMA guidelines. Studies were searched for in PubMed, MEDLINE, EMBASE, and the Cochrane Library. Outcome endpoints included clinical pregnancy and live birth rates (LBRs).

Results: A total of 605 records were retrieved in the initial search. After exclusion, 30 articles were included for further screening for eligibility. For meta-analysis, 1 prospective and 5 retrospective cohort studies were included for pooled analysis, from which clinical pregnancy rates (CPRs) were evaluated in 6 studies while LBRs were evaluated in 3 studies. CPRs were comparable when ICSI was performed at (a) <2 hours POR (risk ratio or RR = 1.00, 95% confidence interval [CI] 0.94–1.08) vs 2+ hours, (b) <3 hours (RR = 1.01, 95% CI 0.88–1.16) vs 3+ hours, (c) <4 hours (RR = 0.99, 95% CI 0.93–1.05) vs 4+ hours, (d) <5 hours (RR = 0.98, 95% CI 0.93–1.02) vs 5+ hours, and (e) <6 hours (RR = 1.05, 95% CI 0.90–1.23) vs 6+ hours. However, LBR was reduced when ICSI was performed <5 hours POR vs 5+ hours (RR = 0.94, 95% CI 0.89–0.99), but such reduction disappeared when comparing <6 hours POR (RR = 1.09, 95% CI 0.85–1.38) vs 6+ hours.

Conclusions: CPRs remain comparable when ICSI is performed at a range of timings up to 6-hour POR. However, LBR may benefit slightly by scheduling ICSI between 5- and 6-hour POR.

***Keywords*:** ICSI; Timing; Meta-Analysis; Live Birth; Clinical Pregnancy.

INTRODUCTION

Following the initial clinical introduction of intracytoplasmic sperm injection (ICSI) in 1992 (Palermo et al., 1992), this approach has been routinely used to treat male factor infertility with great success for the past three decades. It is a robust yet time intensive procedure and has been regarded as one of the critical skillsets in assisted reproductive technology (ART), with expanding usage (Quaas, 2021). However, clinical implications after performing ICSI at different timings post oocyte retrieval (POR) remain poorly understood with a lack of consensus (Rubino et al., 2016). Conflicting data have been reported in the literature, showing diverse effects of ICSI timings on the subsequent fertilization and pregnancy outcomes (Pujol et al., 2018; Vandenberghe et al., 2021; Wang et al., 2021; Zhang et al., 2020). On the other hand, the busy schedule in ART clinics demands flexibility for time consuming procedures such as ICSI, provided it does not compromise treatment outcomes.

The three timings that are believed to be critical in the final maturation process of human oocytes and success of subsequent *in vitro* fertilization (IVF) treatment include (a) ovulation induction or trigger at the end of ovarian stimulation, (b) first polar body extrusion giving rise to metaphase II oocytes, and (c) insemination (via either conventional IVF or ICSI). While oocytes can be inseminated by co-incubation with a certain concentration of motile sperm to allow spontaneous fertilization (i.e., conventional IVF),

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ICSI has been increasingly used worldwide albeit with significantly more staff hours required (Veiga et al., 2022). Also it is often challenging in a busy ART laboratory to conduct procedures at fixed time points, even if a target time point is aimed for (Liu et al., 2022). Unlike conventional IVF where late matured oocytes may have the opportunity to allow sperm penetration at a later time during the extended co-incubation period (e.g. overnight), oocytes undergoing ICSI only passively accept sperm entry following injection regardless of the degree of cytoplasmic maturity (Liu et al., 2015). Whilst it is acknowledged that sufficient maturation time post ovulation trigger is necessary to allow oocytes to complete their first meiosis (Coticchio et al., 2015; Oliveira et al., 2016), it is also believed that excessive incubation prior to fertilization may accompany spindle instability (Pujol et al., 2018). This can lead to adverse outcomes such as poor embryo quality, reduced fertilization rate, and ultimately diminished clinical pregnancy rate (CPR) (Cohen et al., 2004; Petersen et al., 2009; Pujol et al., 2018). However, others reported no adverse effects on both embryological and clinical outcomes following ICSI within a wide range of timings (Vandenberghe et al., 2021), indicating that a wide fertilization window in oocytes could be potentially available. Indeed, time-lapse evidence has clearly demonstrated the within-cohort variation in cytoplasmic maturity of sibling oocytes, despite identical timings of ovulation trigger, oocyte retrieval (OR), and nuclear maturity (Liu et al., 2014). In addition, there appears to be an increasingly blurry definition in the normal developmental timeline of human embryos, an issue that is becoming more prominent in embryology, and a problem that could also be applicable to oocytes (Coticchio et al., 2021). This study aims to systematically review the available literature and perform a meta-analysis using pooled data, studying the effect of ICSI timing POR with endpoints measured by CPRs and live birth rates (LBRs).

METHODS

The protocol for this review was registered with the PROSPECRO (CRD42022296838).

Search strategy/selection criteria

PRISMA guidelines were applied, and the literature was searched on Embase, PubMed, Cochrane Library, and Medline up until December 16, 2021. There was no restriction on publication date, and articles were restricted to those translatable to English involving human subjects. All article types except for review were included. The search strategy used for this systematic analysis was ("subfertile" OR "sub-fertile" OR "infert*" OR "fertility treatment" OR "women" OR "female" OR "couple") AND ("ICSI" OR "intracytoplasmic sperm injection" OR "intra-cytoplasmic sperm injection") AND ("timing" OR "time interval") AND ("pregnancy" OR "fertili*" OR "birth") NOT (Review [Publication Type]). This search strategy produced 605 results. Articles that included clear time intervals between OR and ICSI, raw data with sample sizes, and their impact on the clinical outcomes of CPR and/or LBR were included in the study. Articles focusing on oocyte denudation timing prior to ICSI were excluded. Two independent reviewers (IG and MT) then evaluated each study based on population, intervention, controls, and outcome (PICO) with mediation completed by a third independent reviewer (YL).

Outcomes

The two outcomes of interest were CPR (the number of clinical pregnancies out of the total number of embryo transfers for each subgroup) and LBR (the number of live births out of the total number of embryo transfers for each subgroup). Clinical pregnancy was defined by ultrasound visualization of the gestational sac at approximately 5–7 weeks gestation. Live birth was defined as successful delivery of a live fetus.

Data extraction and risk of bias assessment

Quantitative and qualitative data were extracted independently by two reviewing authors (IG and MT) according to standard Cochrane data extraction methods (Higgins et al., 2022). The Newcastle-Ottawa Scale (NOS) was used to assess the included cohort studies. This was performed by two independent reviewers (IG and MT) and mediation was again completed by a third independent reviewer (YL).

Statistical analysis

Meta-analysis of binary outcomes was performed using the Review Manager Software version 5.4 (Cochrane RevMan). Random effect models using the Mantel–Haenszel method were used to combine the data for CPR and LBR from eligible studies depending on the availability of raw data in corresponding subgroups. A random-effect model was selected to account for studies that estimated different yet related effects. The thresholds of ICSI timing for CPR comparisons were selected at 2-, 3-, 4-, 5-, and 6-hour POR, depending on availability of raw data for pooled analysis. Similarly, ICSI timing thresholds for LBR comparisons were selected at 5- and 6-hour POR due to unavailability of raw data for pooling at other thresholds. The effect size reported was the RR of the earlier to the later ICSI timing POR, along with the 95% confidence interval (CI), displayed in forest plots. The I^2 index was utilized to assess the statistical heterogeneity of the studies, with $I^2 > 50\%$ representing substantial heterogeneity and $I^2 > 75\%$ indicating considerable heterogeneity.

RESULTS

Studies included for quantitative assessment

After removal of duplicates, there were a total of 605 hits found in the literature search. Following initial exclusion according to our PICO, 30 articles were included for full text screening to assess eligibility. Nine were evaluated after full text review, with a further 4 excluded following data extraction. The remaining 5 articles were searched for in-text citations that had extractable data, with another article being selected for inclusion. For meta-analysis, 6 articles were finally included that met the inclusion criteria. The study selection process is displayed in the PRISMA flowchart (Fig. 1). Overall, using a scoring system of 7–9 (low risk of bias), 4–6 (high risk of bias), and 0–3 (very high risk of bias), 4 articles had a low risk of bias, and 2 articles had a high risk of bias (Table 1). Of the 6 studies, one was a prospective cohort study (Azizi et al., 2020) and the remaining 5 were retrospective cohort studies (Carvalho et al., 2020; Esiso et al., 2021; Jacobs et al., 2001; Rienzi et al., 1998; Vandenberghe et al., 2021). The 6 included studies involved multiple centres across different countries with a range of sample sizes.

Pooled analyses on CPR

All 6 included studies were used to analyze the CPR, with raw data for each threshold (2-, 3-, 4-, 5-, or 6-hour POR) where available pooled for separate meta-analyses as shown in Fig. 2. For each set of ICSI timings, the overall effect was not statistically significant, with the RR ranging between 0.88 and 1.23. Further comparisons showed comparable CPRs between ICSI timings of (a) <2 hours vs 2+ hours (2 studies n = 8,566, RR = 1.00, CI 0.94–1.08), (b) <3 hours vs 3+ hours (3 studies n = 8,661, RR = 1.01, CI 0.88–1.16), (c) <4 hours vs 4+ hours (3 studies n = 8,750, RR = 0.99, CI 0.93–1.05), (d) <5 hours vs 5+hours (3 studies n = 15,682, RR = 0.98, CI 0.93–1.02), and (e) <6 hours vs 6+ hours (3 studies n = 7,635, RR = 1.05, CI 0.90–1.23). There was overall low heterogeneity ($I^2 < 50\%$) across all included

Fig. 1. PRISMA flow chart.

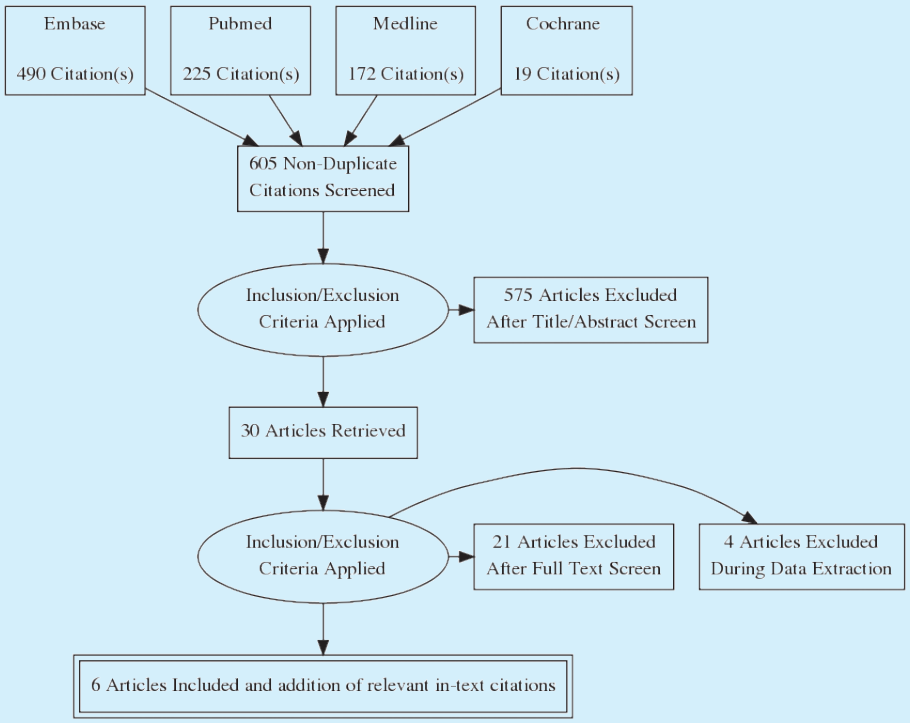

Table 1. Risk of bias NOS scoring.

Studies	Selection (4)	Comparability (2)	Outcome (3)	Total (9)
Azizi et al. (2020)	2	2	3	7
Carvalho et al. (2020)	3	1	3	7
Esiso et al. (2021)	2	1	2	5
Jacobs et al. (2001)	3	1	3	7
Rienzi et al. (1998)	2	1	2	5
Vandenberghe et al. (2021)	3	2	2	7

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data indicating good consistency in findings amongst studies, except for the 6-hour threshold grouping which showed slightly elevated heterogeneity (I^2 = 51%).

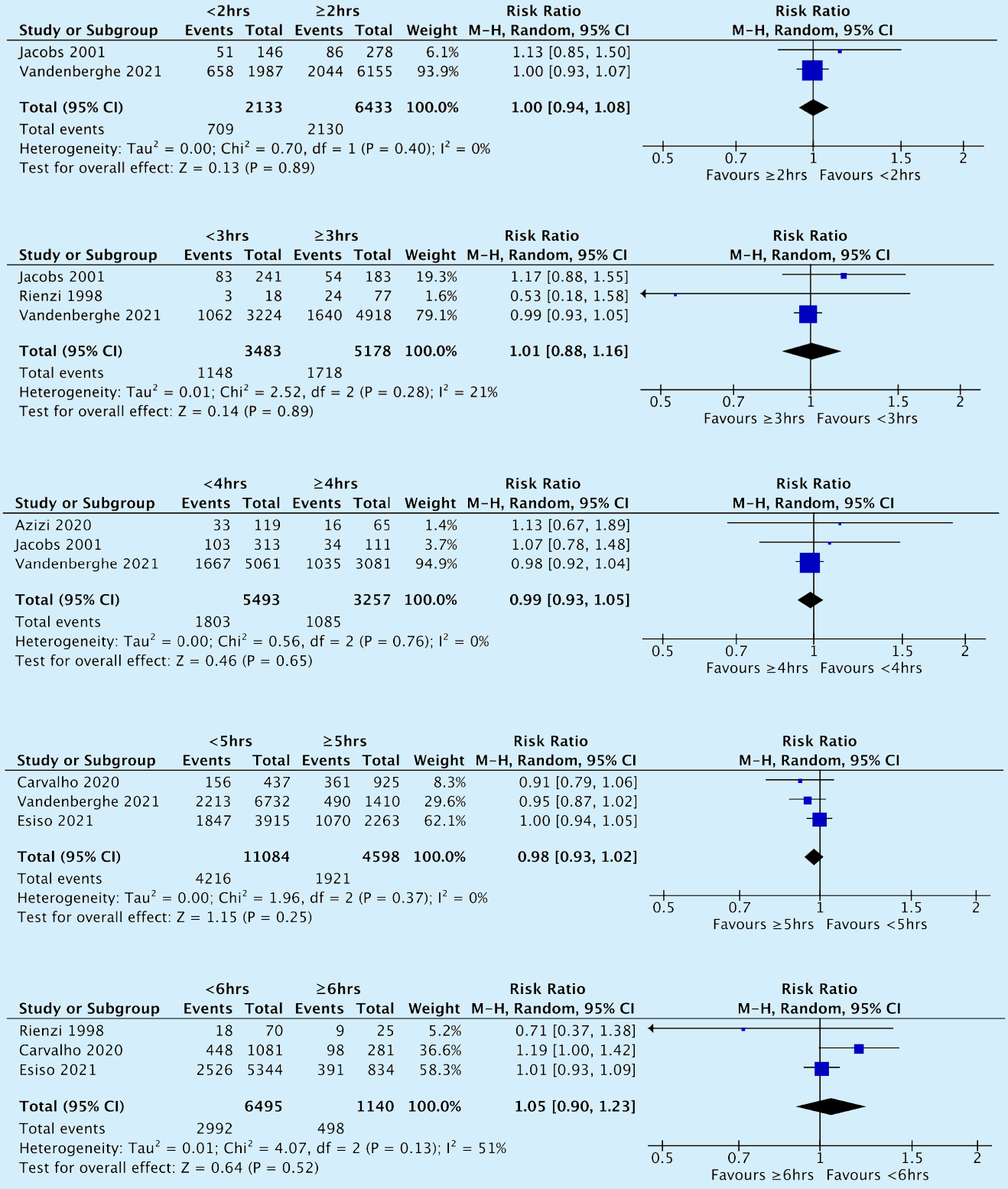
Pooled analyses on LBR

Three of 6 studies reported LBRs, with raw data for each threshold where available (5- or 6-hour POR) pooled for separate meta-analyses as shown in Fig. 3. LBR was significantly lower when ICSI was performed <5 hours (3 studies n = 15,682, RR = 0.94, CI 0.89–0.99) in reference to 5+ hours POR. However, the 6-hour threshold comparison showed similar LBR (2 studies n = 7,540, RR = 1.09, CI 0.85–1.38) between earlier ICSI (<6 hours POR) and later ICSI (+6 hours POR), albeit an opposite trend to the 5-hour threshold. There was no heterogeneity (I^2 = 0%) demonstrated in the data using the 5-hour threshold showing excellent consistency in findings amongst studies. However, data using the 6-hour threshold displayed significant heterogeneity (I^2 = 77%) in the findings between two studies.

DISCUSSION

There is ongoing controversy in the literature surrounding the effect of ICSI timing on the subsequent LBR and CPR. An earlier study has shown no adverse impact of shorter or longer incubation time (ranging from 0.5- to 8-hour POR) prior to ICSI on the subsequent fertilization rate, embryo quality, implantation, and ongoing pregnancy rates (Jacobs et al., 2001). While another group demonstrated beneficial effects of a longer incubation period (>3 hours POR) on the subsequent embryo quality (Rienzi et al., 1998). However, both studies were based on relatively small sample sizes. More recently, evidence based on a larger sample size (n = 3,986), using both fresh and vitrified oocytes, indicated no difference in CPRs and LBRs within a wide range of ICSI timings, from 1 hour 25 minutes

Fig. 2. Forest plots comparing CPRs between different ICSI timing cut-offs POR.



to 17 hours 14 minutes POR (Barcena et al., 2016). This was further supported by an independent group based on 2,051 consecutive fresh autologous ICSI cycles (Naji et al., 2018). Meanwhile, Pujol et al. (2018) reported a progressive decrease in CPR at 7.7% per 1-hour increase in ICSI timing POR (ranging from 1.00 to 12.64 hours, *n* = 1,468). On the contrary, another study with a similar sample size (*n* = 1,378) reported that best outcomes were achieved when ICSI was performed between 5- and 6-hour POR, in terms of CPRs, LBRs, and cumulative LBRs (Carvalho et al., 2020). This window (5- to 6-hour POR) is likely a balance between maximized cytoplasmic maturation in oocytes and minimized cellular aging caused by excessive incubation (Coticchio et al., 2015). In addition, the role played by the cumulus cells during the cytoplasmic maturation process of human oocytes when cultured *in vitro* also

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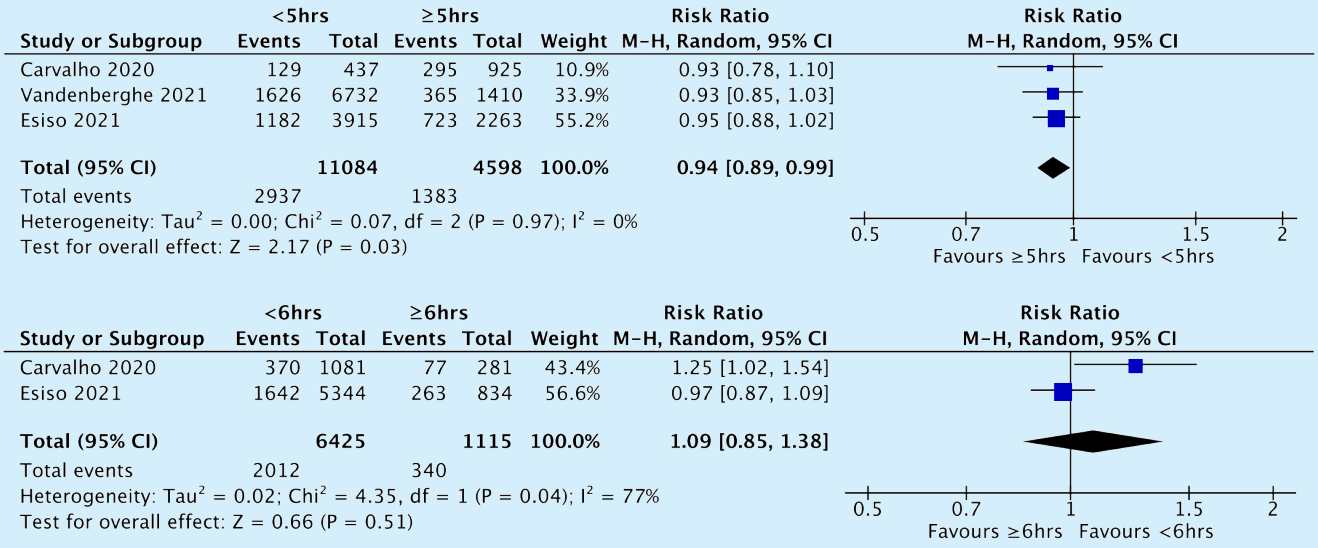
Fig. 3. Forest plots comparing LBRs between different ICSI timing thresholds POR.



remains controversial (Wang et al., 2021). Evidence in animal models indicated the vulnerability of cumulus cells to oxidative stress in prolonged *in vitro* culture, which in turn potentially promotes oocyte aging, causing a series of downstream adverse events (Lian et al., 2013; Miao et al., 2009; Takahashi et al., 2013). There may also be adverse impacts during prolonged incubation of oocytes, caused by laboratory factors such as the additional disruption of culture conditions by excessive opening and closing of incubator doors (Carvalho et al., 2020). A recent systematic review, although in the absence of meta-analysis, suggested that an incubation time greater than 4 hours could result in spindle instability in the oocytes leading to poorer quality embryos (Wang et al., 2021). It is often difficult to investigate longer time intervals prior to ICSI, such as >6 hours POR, because of staff availability for specific work hours. Therefore, ICSI at 2- to 6-hour POR seems to be a reasonable compromise to meet practical needs, although is still under debate (Maggiulli et al., 2020; Patel et al., 2021). This window is further supported by one recent randomized controlled trial (RCT), where no differences were detected in fertilization and blastulation rates between the 2.5- vs 5-hour POR ICSI groups (Smith et al., 2021). However, no CPRs or LBRs were evaluated in this trial. Therefore, at this stage, a CPR and LBR focused meta-analysis based on a pooled dataset would offer strengthened evidence to guide clinical practice.

The current meta-analysis included 5 retrospective and 1 prospective cohort studies. Most excluded studies were due to either (a) having not evaluated CPR or LBR, or (b) absence of raw data for

Table 2. Variations in associated timings in 6 included studies.

Studies	Trigger types	OR timing post trigger	Denudation timing before ICSI
Azizi et al. (2020)	Urinary hCG (Pregnyl, dosage not stated).	Ranging from 35 to 41.7 hours post trigger, reporting no association with pregnancy outcomes.	Comparisons of denudation ≤2 vs >2 hours before ICSI, reporting no differences in regard to pregnancy outcomes.
Carvalho et al. (2020)	Urinary hCG (5,000–10,000 IU Pregnyl), or recombinant hCG (250 IU Ovitrelle).	34–36 hours post trigger.	Comparisons of denudation <1, 1.5–2, and ≥2 hours before ICSI, reporting decreasing cumulative LBRs (37.7%, 37.5%, 30.1%, respectively).
Esiso et al. (2021)	Urinary hCG (10,000 IU Novarel), or recombinant hCG (250 μg Ovidrel), or GnRH agonist (Leuprolide acetate, but dosage not stated) as per reference referred in text.	36 hours post trigger.	Immediately before ICSI.
Jacobs et al. (2001)	Urinary hCG (Pregnyl, dosage not stated).	36 hours post trigger.	Immediately before ICSI.
Rienzi et al. (1998)	hCG (neither origin nor dosage stated).	36 hours post trigger.	Immediately before ICSI.
Vandenberghe et al. (2021)	Urinary hCG (5,000 or 10,000 IU Pregnyl), or recombinant hCG (250 IU Ovitrelle), or GnRH agonist (0.2 mg Decapeptyl or Gonapeptyl).	36 hours post trigger except for the "<36 h ICSI" group.	Immediately before ICSI.

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pooled analysis at different cut-offs. Our pooled analysis indicated a potential benefit in terms of LBR (RR = 0.94, 0.89–0.99) when delaying ICSI until 5+ hours POR. Such effect was lost (RR = 1.09, 0.85–1.38) when ICSI was performed 6+ hours POR. Unfortunately, we were unable to perform LBR comparisons using cut-offs other than the 5- and 6-hour thresholds, due to the unavailability of raw data for pooling. But a series of CPR comparisons using 2- to 6-hour cut-offs did not detect any significant difference.

The biological clock in human oocytes following ovulation trigger is still poorly understood. It is important to highlight that in clinical practice there are variations in (a) the ovulation trigger strategies, (b) OR/denudation timings, and (c) the maturity (both nuclear and cytoplasmic) status between even sibling oocytes (Rubino et al., 2016). Our previous study has demonstrated a large variation in the timings of second polar body extrusion in oocytes post ICSI, confirming the inter- and intra-cohort variation in oocyte cytoplasmic maturity despite the fact that all oocytes had achieved nuclear maturity as indicated by the presence of the first polar body (Liu et al., 2014). Such discrepancy is thought to arise from different sizes of follicles at trigger injection (Revelli et al., 2014). The reported trigger timing for ovulation induction also varies, mostly ranging between 34 and 38 hours before OR; but the 36-hour trigger approach seemed to be most common. For this study, we aimed for all included articles to have used a 36-hour trigger approach, however 2 of the 6 studies had timings varying between 35–41.7 hours (Azizi et al., 2020) and 34–36 hours (Carvalho et al., 2020) (Table 2). Such variations may lead to different biological arrangements of the oocytes that are inseminated via conventional IVF or ICSI. This variance may therefore be a confounding factor when pooling data to compare the effect of timing on CPR and LBR. Oocytes at various maturity (both nuclear and cytoplasmic) stages are exposed to sperm for an extended period of time (e.g., overnight) while undergoing IVF insemination, allowing additional opportunities to complete final maturation before sperm entry (Jacobs et al., 2001). Contrastingly, sperm entry at an artificially determined procedural timing, that is, ICSI timing, may potentially result in diverse biological responses in the oocytes with different cytoplasmic maturity. The conflicting effects of ICSI timing reported in literature are likely a consequence of inter-institute variations in their protocols such as follicle size measurement, trigger timing/dose/type, ICSI timing recorded (such as at start time or end time of the procedure), or a combination. The underlying mechanism of the observed difference in this study regarding LBR but not CPR could be a result of longer-term manifestation of such effects. Future studies should focus on neonatal outcomes such as birth weight and gestational age.

Cumulative LBR would be a preferred measure as CPR and LBR following fresh transfer only reflect prognosis of the specific embryo(s) selected for transfer instead of the entire cohort. In our search, there was only one study that reported cumulative LBR so pooled analysis could not be performed (Carvalho et al., 2020). However, our findings in LBR were in line with the aforementioned study, where cumulative LBR was significantly higher when ICSI was performed at 5- to 6-hour POR (36.6%) in reference to 6+ hours (27.7%).

There were several limitations in this study. First, not all 6 included articles could be used to determine both endpoints of this study. LBR is a widely accepted preferred endpoint, but only 2 ICSI timing cut-offs were available for comparison in our pooled analysis. Therefore, more evidence is required in future studies to gain a better insight by including a fuller cut-off range. An additional limitation is that the retrospective cohort studies included for pooled analysis are considered lower quality evidence and may involve the element of publication bias. There is also significant heterogeneity in the 6-hour LBR grouping with an $I^2 > 77\%$ and the 6-hour CPR grouping with an $I^2 > 51\%$. The heterogeneity could be due to the smaller sample size in the data. Also, data for both groupings were collected from three single centre retrospective cohort studies, which may have had confounders that had not been controlled for through their respective data collection. This meta-analysis has only focused on the ICSI timing POR, the timing of most interest as per amount of publication. Variations in other associated timing parameters in each of the 6 studies are summarized in Table 2. The role of denudation was also not heavily focused on in this study, with variations in timing of denudation in relation to OR and ICSI in the included studies, which may be a potential confounder to LBR and CPR analysis. Trigger timings were not completely consistent amongst included studies, which is also considered a potential confounder to our meta-analysis.

Despite the limitations, there are numerous strengths to this meta-analysis. This is one of few studies to directly address the effect of ICSI timings on LBR and CPR. Also, having multiple cut-offs for time groupings in the meta-analyses allows for the data to be analyzed in the most comprehensive manner. Our results enabled a further step forward based on the foundation of previous systematic reviews (Rubino et al., 2016; Wang et al., 2021), by performing pooled analysis, potentially leading to a data-based advancement over conflicting reports in literature. For future studies, time-lapse analysis would assist in better understanding the linkage between ICSI timing and subsequent developmental milestones, for example, pronuclear fading (Liu et al., 2015). Indeed, evidence from known implanting human embryos confirmed certain degree of variance tolerance in terms of early morphokinetic profiles (Liu et al., 2015). The inclusion of fertilization and blastulation rates were not included in this paper due to a focus on the clinical endpoints of the ICSI cycle, however there is merit in including these outcomes in future studies. Greater standardization regarding steps in the ICSI procedure is also demanded to generate better quality datasets, with the inclusion of as many potential confounders as possible to facilitate unbiased interpretation of results. Again, RCTs remain the preferred path to generate the highest quality of data, which would add value into future systematic reviews and meta-analyses.

In conclusion, no significant differences were detected in CPRs between different ICSI timings up to 6-hour POR. There may be a potential benefit in LBR when ICSI was performed at 5- to 6-hour POR.

CONFLICT OF INTEREST STATEMENT

The authors disclose no financial or nonfinancial conflicts of interests in this study.

REFERENCES

Azizi E, Naji M, Nazarian H, et al. Does timing in ICSI cycle affect oocyte quality and reproductive outcomes? A prospective study. Arch Gynecol Obstet. 2020;302:505–13.

Barcena P, Rodriguez M, Obradors A, et al. Should we worry about the clock? Relationship between time to ICSI and reproductive outcomes in cycles with fresh and vitrified oocytes. Hum Reprod. 2016;31:1182–91.

Bosdou JK, Kolibianakis EM, Venetis CA, et al. Is the time interval between HCG administration and oocyte retrieval associated with oocyte retrieval rate? Reprod Biomed Online. 2015;31:625–32.

Carvalho M, Leal F, Mota S, et al. The effect of denudation and injection timing in the reproductive outcomes of ICSI cycles: new insights into the risk of *in vitro* oocyte ageing. Hum Reprod. 2020;35:2226–36.

Cohen Y, Malcov M, Schwartz T, et al. Spindle imaging: a new marker for optimal timing of ICSI? Hum Reprod. 2004;19:649–54.

Coticchio G, Barrie A, Lagalla C, et al. Plasticity of the human preimplantation embryo: developmental dogmas, variations on themes and self-correction. Hum Reprod Update. 2021;27:848–65.

Coticchio G, Dal Canto M, Mignini Renzini M, et al. Oocyte maturation: gamete–somatic cells interactions, meiotic resumption, cytoskeletal dynamics and cytoplasmic reorganization. Hum Reprod Update. 2015;21:427–54.

Esiso FM, Cunningham D, Lai F, et al. The effect of rapid and delayed insemination on reproductive outcome in conventional insemination and intracytoplasmic sperm injection *in vitro* fertilization cycles. J Assist Reprod Genet. 2021;38:2697–706.

Higgins JPT, Thomas J, Chandler J, et al. (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from: www.training.cochrane.org/handbook

Jacobs M, Stolwijk AM, Wetzels AM. The effect of insemination/injection time on the results of IVF and ICSI. Hum Reprod. 2001;16:1708–13.

Lian HY, Gao Y, Jiao GZ, et al. Antioxidant supplementation overcomes the deleterious effects of maternal restraint stress-induced oxidative stress on mouse oocytes. Reproduction. 2013;146:559–68.

Liu Y, Chapple V, Feenan K, et al. Time-lapse videography of human embryos: using pronuclear fading rather than insemination in IVF and ICSI cycles removes inconsistencies in time to reach early cleavage milestones. Reprod Biol. 2015;15:122–5.

Liu Y, Chapple V, Roberts P, et al. Time-lapse videography of human oocytes following intracytoplasmic sperm injection: events up to the first cleavage division. Reprod Biol. 2014;14:249–56.

Liu Y, Copeland C, Stevens A, et al. Assessment of human embryos by time-lapse videography: a comparison of quantitative and qualitative measures between two independent laboratories. Reprod Biol. 2015;15:210–16.

Liu Y, Ong K, Korman I, et al. The effect of day 5 blastocyst assessment timing on live birth prediction and development of a prediction algorithm. Reprod Biomed Online. 2022;44:609–16.

Maggiulli R, Cimadomo D, Fabozzi G, et al. The effect of ICSI-related procedural timings and operators on the outcome. Hum Reprod. 2020;35:32–43.

Miao YL, Kikuchi K, Sun QY, et al. Oocyte aging: cellular and molecular changes, developmental potential and reversal possibility. Hum Reprod Update. 2009;15:573–85.

Naji O, Moska N, Dajani Y, et al. Early oocyte denudation does not compromise ICSI cycle outcome: a large retrospective cohort study. Reprod Biomed Online. 2018;37:18–24.

Nargund G, Reid F, Parsons J. Human chorionic gonadotropin-to-oocyte collection interval in a superovulation IVF program. A prospective study. J Assist Reprod Genet. 2001;18:87–90.

Oliveira SA, Calsavara VF, Cortes GC. Final oocyte maturation in assisted reproduction with human chorionic gonadotropin and gonadotropin-releasing hormone agonist (dual trigger). JBRA Assist Reprod. 2016;20:246–50.

Palermo G, Joris H, Devroey P, et al. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet. 1992;340:17–18.

Patel G, Singh N, Sethi A. Is 2–6 h optimal window for ICSI? J Assist Reprod Genet. 2021;38:2803–4.

Petersen CG, Oliveira JB, Mauri AL, et al. Relationship between visualization of meiotic spindle in human oocytes and ICSI outcomes: a meta-analysis. Reprod Biomed Online. 2009;18:235–43.

Pujol A, Garcia D, Obradors A, et al. Is there a relation between the time to ICSI and the reproductive outcomes? Hum Reprod. 2018;33:797–806.

Quaas AM. ICSI for non-male factor: do we practice what we preach? J Assist Reprod Genet. 2021;38:125–7.

Revelli A, Martiny G, Delle Piane L, et al. A critical review of bi-dimensional and three-dimensional ultrasound techniques to monitor follicle growth: do they help improving IVF outcome? Reprod Biol Endocrinol. 2014;12:107.

Rienzi L, Ubaldi F, Anniballo R, et al. Preincubation of human oocytes may improve fertilization and embryo quality after intracytoplasmic sperm injection. Hum Reprod. 1998;13:1014–19.

Rubino P, Vigano P, Luddi A, et al. The ICSI procedure from past to future: a systematic review of the more controversial aspects. Hum Reprod Update. 2016;22:194–227.

Smith MB, Ho JR, Cortessis V, et al. What is the optimal timing of intracytoplasmic sperm injection (ICSI) after EGG retrieval? A randomized controlled trial. J Assist Reprod Genet. 2021;38:2151–6.

Takahashi T, Igarashi H, Amita M, et al. Molecular mechanism of poor embryo development in postovulatory aged oocytes: mini review. J Obstet Gynaecol Res. 2013;39:1431–9.

Vandenberghe LTM, Santos-Ribeiro S, De Munck N, et al. Expanding the time interval between ovulation triggering and oocyte injection: does it affect the embryological and clinical outcome? Hum Reprod. 2021;36:614–23.

Veiga E, Olmedo C, Sanchez L, et al. Recalculating the staff required to run a modern assisted reproductive technology laboratory. Hum Reprod. 2022.

Wang X, Xiao Y, Sun Z, et al. Effect of the time interval between oocyte retrieval and ICSI on embryo development and reproductive outcomes: a systematic review. Reprod Biol Endocrinol. 2021;19:34.

Zhang Y, Ma Y, Fang Z, et al. Performing ICSI within 4 hours after denudation optimizes clinical outcomes in ICSI cycles. Reprod Biol Endocrinol. 2020;18:27.

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