In vitro fertilisation (IVF) versus intracytoplasmic sperm injection (ICSI) in patients without severe male factor infertility: study protocol for the randomised, controlled, multicentre trial INVICSI

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ABSTRACT

Introduction Over the last decades, the use of intracytoplasmic sperm injection (ICSI) has increased, even among patients without male factor infertility. The increase has happened even though there is no evidence to support that ICSI results in higher live birth rates compared with conventional in vitro fertilisation (IVF) in cases with nonmale factor infertility. The lack of robust evidence on an advantage of using ICSI over conventional IVF in these patients is problematic since ICSI is more invasive, complex and requires additional resources, time and effort. Therefore, the primary objective of the IVEF versus ICSI (INVICSI) study is to determine whether ICSI is superior to standard IVF in patients without severe male factor infertility. The primary outcome measure is first live birth from fresh and frozen-thawed transfers after one stimulated cycle. Secondary outcomes include fertilisation rate, ongoing pregnancy rate, birth weight and congenital anomalies.

Methods and analysis This is a two-armed, multicentre, randomised, controlled trial. In total, 824 couples/women with infertility without severe male factor will be recruited and allocated randomly into two groups (IVF or ICSI) in a 1:1 ratio. Participants will be randomised in variable block sizes and stratified by trial site and age. The inclusion criteria are (1) no prior IVF/ICSI treatment, (2) male partner sperm with an expected count of minimum 2 million progressive motile spermatozoa following density gradient purification on the day of oocyte pick up and (3) age of the woman between 18 and 42 years.

Ethics and dissemination The study will be performed in accordance with the ethical principles in the Helsinki Declaration. The study is approved by the Scientific Ethical Committee of the Capital Region of Denmark. Study findings will be presented, irrespective of results at international conferences and submitted for publication in peer-reviewed journals.

Trial registration number NCT04128904. Pre-results.

Strengths and limitations of this study

► This is a randomised controlled trial with concealment of treatment allocation, stratification for age and trial site and use of variable block sizes reducing the risk of selection bias and confounding.
► The large number of subjects included and the multicentre approach of the study increases generalisability of the results.
► The primary outcome is first live birth episode ensuring maximum clinical impact.
► Only first-cycle patients are included to avoid selection bias based on the knowledge of results from previous treatment cycles.
► The study is not blinded neither to study participants nor clinicians, which could potentially introduce bias.

INTRODUCTION

Since the introduction of intracytoplasmic sperm injection (ICSI) in the early 1990s,1 the use of ICSI has continuously increased and it is now used widely for indications other than male factor infertility. The latest reports from the European Society of Human Reproduction and Embryology (ESHRE) and The International Committee Monitoring-Assisted Reproductive Technologies (ICMART) show that in Europe and globally, ICSI is used in around two-thirds of all fresh-assisted reproductive technology (ART) cycles.2 3 The ICMART report further accentuates the significant disparities that exists in ART practices across countries. An especially high ICSI:in vitro fertilisation (IVF) ratio is found in the Middle East where the proportion of ICSI cycles in some countries is now 100% of all fresh cycles. It is unlikely that the large disparities
between countries can be explained by differences in the prevalence of male factor infertility alone. In the USA, a recent study, including data from 2000 to 2014, showed a substantial increase (52% increase) in the use of ICSI with no corresponding increase in couples treated for male factor infertility. Likewise, another US study found that the largest increase in the use of ICSI between 1996 and 2012 (from 36% in 1996 to 76% in 2012) was observed among couples without male factor infertility (from 15% to 67%). The observed increase has happened despite the fact that the use of ICSI for nonmale factor infertility remains controversial. While ICSI has resulted in high success rates in couples treated for severe male factor infertility, studies have indicated that ICSI offers no advantage over conventional IVF in nonmale factor infertility couples when it comes to live birth rates. Moreover, the American Society for Reproductive Medicine recently published a committee opinion stating that ‘in cases without male factor infertility or a history of prior fertilisation failure, the routine use of ICSI for all oocytes is not supported by the available evidence’. In the US study from 2018, the large increase in use of ICSI was correlated with a 7.6% (p<0.001) increase in live birth rates per cycle in women younger than 35 years. When including only data from the most recent years (2008–2014), the correlation between ICSI rates and live birth rates disappeared. Questioning whether the ICSI method is responsible for the increased live birth rate. The increased use of ICSI without the presence of male factor infertility could be attributed to a general belief that ICSI decreases the risk of fertilisation failure in patients treated for other indications. Indeed, a systematic review and meta-analysis from 2013 reported higher fertilisation rates and a lower risk of fertilisation failure after ICSI compared with conventional IVF in patients with the routine use of ICSI for unexplained infertility. Yet, many of the included studies did not ascertain their findings with an improvement in clinical outcome (often due to the general belief that ICSI decreases the risk of fertilisation failure in patients treated for other indications). One group of people who might benefit from ICSI are non-male factor infertility patients with a history of total fertilisation failure or low fertilisation. One group of people who might benefit from ICSI are non-male factor infertility patients with a history of total fertilisation failure or low fertilisation. In conclusion, there are still significant gaps in the knowledge regarding ICSI versus conventional IVF for couples with normal and nonsevere male factor infertility. Especially when including considerations of cost (either for the individual patient or for the public healthcare system) and complexity of the methods. The purpose of the IVF versus ICSI (INVICSI) study is to address this knowledge gap and to infer whether ICSI is more effective than standard IVF in patients without severe male factor infertility. The primary outcome measure is first live birth.

**METHODS AND ANALYSIS**

**Hypothesis**

ICSI is superior to standard IVF for obtaining live birth of a child in fertility patients without severe male factor infertility.

**Study design**

The INVICSI study is a multicentre, randomised, controlled trial using a parallel arm design to detect whether ICSI is superior to standard IVF in patients without severe male factor infertility. Patients will be randomised (1:1) to receive insemination of their retrieved eggs with either standard IVF or ICSI. Trial registration data are displayed in Table 1. Table 2 provides an overview of revision chronology including current protocol date and version identifier. Protocol modifications are registered continuously on ClinicalTrials.gov. The SPIRIT reporting guidelines were used.

**Setting**

The trial will be conducted in six public fertility clinics in Denmark. All clinics are part of a university hospital setting and all hospitals perform standardised treatments according to the public healthcare system in Denmark. The teams recruiting patients at the trial sites will include fertility doctors, nursing staff and embryologists. Patient enrolment began in November 2019 and will continue until December 2023.

**Eligibility criteria**

All couples/women referred for their first fertility treatment at six public fertility clinics in Denmark are screened for eligibility with the following inclusion and exclusion criteria:

**Inclusion**

1. Written informed consent.
2. Age of the woman 18–42 years.
3. Body mass index of the woman between 18 kg/m² and 35 kg/m².
4. First fertility treatment due to:
   i. Male partner with normal or non-severely decreased sperm parameters where the semen sample (following density gradient purification) on the day of oocyte pick up (OPU) is expected to contain a minimum of 2 million progressive motile spermatozoa.
   ii. Couples/single using donor sperm.
   iii. Tubal factor.
   iv. Endometriosis.
   v. Unexplained infertility.
   vi. Polycystic ovary syndrome.
   vii. Ovarian reserve.
   viii. Male factor infertility.
   ix. History of prior fertilisation failure.
   x. Severe male factor infertility.
   xi. Low fertilisation rate.
   xii. Unexplained infertility.

**Exclusion**

1. Women with a history of infertility where ICSI has resulted in fertility after treatment with conventional IVF.
2. Patients treated for other indications.
3. Patients treated for severe male factor infertility.
4. Patients with severe male factor infertility.
## Table 1 Trial registration data

| Data category                                      | Information                                                                                                                                 |
|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Primary registry and trial identifying number     | ClinicalTrials.gov ID: NCT04128904, Protocol ID: INVICSI2019                                                                               |
| Date of registration in primary registry          | 10 July 2019                                                                                                                                  |
| Secondary identifying numbers                     | H-19022201                                                                                                                                   |
| Source(s) of monetary or material support         | Capital Region of Denmark, Gedeon Richter                                                                                                   |
| Primary sponsor                                    | Copenhagen University Hospital Hvidovre                                                                                                      |
| Secondary sponsor(s)                              | None                                                                                                                                         |
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| Public title                                      | INVICSI–IVF vs ICSI in patients without severe male factor infertility                                                                     |
| Scientific title                                  | IVF vs ICSI in patients without severe male factor infertility (INVICSI): a randomised, controlled, multicentre trial                        |
| Countries of recruitment                          | Denmark                                                                                                                                     |
| Health condition(s) or problem(s) studied         | Methods of insemination (ICSI vs conventional IVF), infertility without severe male factor                                                    |
| Intervention(s)                                   | Active comparator: insemination with ICSI, Active comparator: insemination with conventional IVF, Randomisation 1:1 to receive insemination with ICSI or conventional IVF |
| Key inclusion and exclusion criteria              | Inclusion: age of the woman 18–42 years, BMI of the woman between 18–35 kg/m², male partner with normal or non-severely decreased sperm parameters or use of donor sperm |
|                                                    | Exclusion: previous IVF or ICSI treatments with current partner, use of donor oocytes or frozen oocytes, ovarian cysts >4 cm, known liver or kidney disease, unregulated thyroid disease, endometriosis stage 3–4, hypogonadotropic hypogonadism, other severe comorbidity (eg, diabetes or cardiovascular disease) |
| Study type                                        | Randomised controlled multicenter trial using a parallel arm design. Randomisation 1:1 to receive insemination with ICSI or conventional IVF |
| Date of first enrolment                           | November 29, 2019                                                                                                                             |
| Target sample size                                | 824                                                                                                                                          |
| Recruitment status                                | Recruiting                                                                                                                                   |
| Primary outcome(s)                                | First live birth rate: the number of first live birth episodes from the study oocyte collections including transfer of fresh- and frozen-thawed embryos |
| Key secondary outcomes                            | Cycles with total fertilisation failure, fertilisation rate, embryo quality, positive pregnancy test rate, ongoing pregnancy rate, pregnancy loss rate, all live birth episodes, preterm delivery, birth weight and congenital anomalies |

ICSI, intracytoplasmic sperm injection; INVICSI, IVF versus ICSI; IVF, in vitro fertilisation.
A regular menstrual cycle was removed as current evidence suggests that women with PCOS have similar chances of conceiving with fertility treatment compared with women without PCOS.²⁰⁻³¹

In September 2019, the criterion for a diagnostic semen sample with a minimum of 5 million progressive motile spermatozoa was also removed (after the inclusion of 88 participants). Due to differences in laboratory techniques and standard tests performed prior to IVF/ICSI on the trial sites, it was not feasible to include a criterion for a diagnostic semen sample. The criterion for number of spermatozoa in the semen sample on the day of OPU remained unchanged.

### Screening, inclusion and consent

Potentially eligible patients receive verbal and written information about the study by the investigators during a consultation in the fertility clinic. Inclusion and randomisation of participants to either ICSI or conventional IVF take place after the ovulation trigger has been prescribed and before the oocyte collection. This is to avoid the risk of the allocation group (IVF or ICSI) affecting the clinicians’ choice when deciding the dose of the follicle-stimulating hormone as well as the timing (or cancellation) of oocyte collection. Also, this ensures that the decision for inclusion is not based on the number of oocytes collected. Couples/women who wish to participate in the trial are asked to sign an informed consent form prior to enrolment. They will usually have a minimum of 2 days between receiving the information and deciding whether they wish to participate in the study or not. When a patient has given consent and inclusion criteria are met, randomisation is conducted in the online platform REDCap, which is also used for data collection during the study.³² The REDCap database has a complete audit trail and is based on anonymous subject ID numbers. It is not revealed whether the patient is assigned to standard IVF or ICSI until after the patient has been recruited and baseline data have been entered in REDCap ensuring treatment allocation concealment. Participants can withdraw from

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**Table 2  Protocol, revision chronology**

| Version     | Date of approval | Primary reasons for amendment                                                                 |
|-------------|------------------|------------------------------------------------------------------------------------------------|
| Original    | August 8, 2019   |                                                                                                 |
| Amendment 1 | January 28, 2020 | Removed inclusion criteria: (i) regular menstrual cycles (21–35 days). (ii) Diagnostic sperm sample from the male partner with ≥4% morphologically normal spermatozoa Added section: handling of poor semen sample on the day of OPU |
| Amendment 2 | March 20, 2020   | Removed inclusion criteria: treatment with donor sperm or male partner sperm with a minimum concentration of 5 million progressive motile spermatozoa in a (purified) diagnostic semen sample. Added inclusion criteria: male partner with normal or non-severely decreased sperm parameters where the sperm sample (purified) on the day of oocyte pick up is expected to contain a minimum of 2 million progressive spermatozoa. |
| Amendment 3 | September 2, 2020| New trial site added (The Fertility Clinic, Zealand University Hospital)                          |
| Amendment 4 | September 16, 2020| Removed inclusion criteria: treatment with donor sperm or male partner sperm with a minimum concentration of 5 million progressive motile spermatozoa in a (purified) diagnostic semen sample. Added inclusion criteria: male partner with normal or non-severely decreased sperm parameters where the sperm sample (purified) on the day of oocyte pick up is expected to contain a minimum of 2 million progressive spermatozoa. |

OPU, oocyte pick up.

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ii. Unexplained infertility.
iii. Polycystic ovary syndrome (PCOS).
iv. Light to moderate decreased semen quality in the male partner.

Exclusion
1. Consent not obtained.
2. Significant morbidity in the woman:
   i. Ovarian cysts ≥4 cm.
   ii. Known liver or kidney disease.
   iii. Unregulated thyroid disease.
   iv. Endometriosis stage 3–4.
   v. Hypogonadotropic hypogonadism.
   vi. Other severe comorbidity (eg, diabetes or cardiovascular disease).
3. Previous IVF or ICSI treatments with current partner.
4. Use of donor oocytes or frozen oocytes.
5. Not speaking or understanding Danish or English language.

Couples using sperm from the male partner as well as couples (or single women) using donor sperm are eligible. Subsequently, randomisation and inclusion will be based on data from the female participant receiving the ovarian stimulation treatment.

The study was originally designed and performed with the additional inclusion criteria of regular menstrual cycles (21–35 days) and a diagnostic sperm sample from the male partner with a minimum of 5 million progressive motile spermatozoa and ≥4% morphologically normal spermatozoa (table 2). However, an amendment was added after the inclusion of 28 participants in May 2020. In this amendment, two of the aforementioned criteria were removed (regular menstrual cycle and minimum percentage of morphological normal sperm). The criterion for sperm morphology was removed because the importance of sperm morphology and whether it should be used to predict fertilisation and reproductive outcome in ART has been questioned.²⁴⁻²⁸ The criterion for regular menstrual cycle was removed as current evidence

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the trial at any time without giving an explanation, and their fertility treatment will not be affected.

Randomisation
An independent statistician prepared the computer-generated randomisation scheme in a 1:1 ratio between the two arms (IVF and ICSI). Permutated blocks of variable size between 4 and 12 were used for randomisation. The randomisation scheme was stratified by trial site and female age (three age groups: 18–25 years of age, 26–37 years of age and 38–41 years of age) to ensure that the number of participants receiving IVF and ICSI is closely balanced within each stratum. The randomisation procedure is performed online in REDCap. The allocation table was uploaded in REDCap by the independent statistician and concealed from the clinical staff performing the randomisation. The unique Danish social security number of each participant is entered initially ensuring that no participants are randomised two times.

Poor semen sample on the day of OPU
If the purified semen sample contains less than 2 million progressive spermatozoa on the day of OPU, the woman/couple will be treated with ICSI regardless of allocation.

Blinding
The study is designed with no blinding of participants, clinicians or assessors. It was decided not to blind clinicians and participants as our experience shows that patients in the Danish fertility clinics are eager to know the insemination method used in their treatment. Hence, it was deemed unrealistic to recruit participants if allocation was only revealed after the endpoints were reached.

Intervention
The participants will receive conventional IVF or ICSI treatment as determined by randomisation. Both treatments are part of standard treatment regimens at the trial sites.

The fertility treatment
The women have been treated in either a short gonadotropin-releasing hormone (GnRH)-agonist protocol or a long GnRH-agonist protocol for ovarian stimulation. The controlled ovarian stimulation, transvaginal ultrasound examinations and the ovulation triggering are done according to the usual daily practice at the trial sites which normally entails ovulation trigger being prescribed when a minimum of two to three follicles measure 17 mm or more. However, women with only one mature follicle may also be prescribed the ovulation trigger. OPU is performed 36±2 hours after the ovulation trigger is administered. On the day of OPU, the concentrations of all spermatozoa and progressive motile spermatozoa is assessed in the ejaculate. Following density gradient purification, wash steps and resuspension in 1 mL media, the number of all spermatozoa as well as the number of progressive motile spermatozoa are assessed again. In cases with a high concentration of spermatozoa in the ejaculate, it is allowed to purify only part of the sample. In this case, a theoretical (after purification) total yield is calculated.

Oocyte insemination will be IVF or ICSI according to randomisation, using established procedures at the trial sites. However, short time insemination in the IVF arm is not allowed. In case of total fertilisation failure, rescue ICSI is not performed. Embryo culture and luteal phase support will follow the usual procedures at each trial site. Blastocyst transfer is performed on day 5. Patients with a poor ovarian reserve and few oocytes retrieved (≤4) are allowed transfer day 2 or 3 according to clinical practice. Single embryo transfers are planned. Surplus blastocysts of good quality are vitrified on day 5 or 6. Transfer and cryopreservation are done according to usual practice at each trial site. In cases with total freeze of all blastocysts due to the risk of ovarian hyperstimulation syndrome, women are not excluded from the trial. In cases where all blastocysts or spare blastocysts are vitrified, these are transferred in subsequent frozen-thawed embryo transfer (FET) cycles according to the daily practice at each trial site (i.e., natural cycles, substituted or stimulated FET cycles).

Urine pregnancy test or a serum pregnancy test is done at 11–16 days after embryo transfer. If pregnancy is achieved, a transvaginal ultrasound scan is performed at pregnancy week 7–9 to confirm an ongoing and intrauterine pregnancy.

Women will be asked to inform the clinic of the result of the pregnancy as is the usual procedure in the clinic.

Study outcomes
Primary endpoint
The primary endpoint for the INVICSI trial is the first live birth episode following the study cycle in each of the two groups (IVF and ICSI). This is defined as the first live birth from the oocyte collection and includes transfer of fresh embryos and frozen-thawed embryos. The minimum follow-up time will be 1 year after inclusion. Live birth is defined as the delivery of one or more living infants ≥22 weeks of gestation. When the primary endpoint is achieved, further live births from the oocyte collection will not be included in the primary outcome analysis. Subsequent live births from any FET cycles with embryos from the first fresh cycle are included as a secondary outcome (all live birth episodes). The secondary outcomes are summarised in Table 3.

Data collection methods
Before treatment is initiated all fertility patients in the clinics fill out a standard form including data on fertility and medical history, ethnicity, medications, smoking, alcohol, height, weight and so on. These data are routinely entered into electronic medical files of the fertility clinics by fertility doctors prior to the patients first consultation in the clinic. This is part of standard practice for all fertility patients. For the INVCISI study, baseline data will be gathered by the investigators from the

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electronic files after written informed consent has been given (age, weight, height, ethnicity, antral follicle count, antimüllerian hormone concentration, years of infertility, primary or secondary infertility, infertility diagnosis, stimulation protocol, sperm characteristics). Data will then be entered into REDCap after which the randomisation and allocation to either standard IVF or ICSI will occur. Data on treatment outcome including fertilisation, embryo development, pregnancy and pregnancy loss (secondary outcomes, table 3) will be collected and entered in REDCap. The couple/woman is asked to consent to data being obtained from the child’s file in case the fertility treatment results in the birth of a living child.

To ensure data collection, an investigator will follow-up on all participants who get pregnancy. Follow-up will take place 1 year after the ultrasound scan (weeks 7–9). If the participant has informed the fertility clinic on birth and child, an investigator will contact the participant via a phone call or retrieve all information from the electronic patient record.

**Statistical considerations**

**Proposed sample size**

The rate of first live births after transfer of up to all of the transferable embryos from the first OPU is set to 45% in the conventional IVF group and 55% in the ICSI group. This is a superiority trial with a power of 80% and a two-sided p value of 5%. The sample size is estimated to be 392 patients in each group. Postrandomisation exclusion is expected to be 5%, resulting in a total of 824 patients.

**Data analysis**

ITT (Intention-To-Treat) analysis and per-protocol analysis will be performed. Baseline characteristics and outcomes will be compared using t-test, Mann-Whitney U test or χ² tests for continuous and categorical variables or logistic regression analysis, controlling for possible confounding effects where appropriate. P values of <0.05 will be considered statistically significant. Statistical analyses will be performed by an investigator together with statistical experts. The primary RCT analysis will be performed by an independent statistician blinded to group allocation.

**Ethics and dissemination**

**Data security and ethical aspects**

Data to describe the study population and the outcomes will be collected in a single database including all participants with an identification code, which makes every participant anonymous in the database.

The study is approved by the Scientific Ethical Committee of the Capital Region of Denmark (H-19022201) and the Danish Knowledge Centre on Data Protection Compliance. The study will be performed according to the Danish Law and Ethical principles in the Helsinki Declaration. Each participant will receive oral and written information about the study and will have opportunity for time and reflection. They can also discuss their participation with a third person. The collected oocytes of the participants will be fertilised with IVF or ICSI according

**Table 3  Secondary outcomes**

| Outcome     | Assessment                                                                 |
|-------------|-----------------------------------------------------------------------------|
| Fertilisation | Fertilisation rate per aspirated oocyte retrieved (16–20 hours after IVF/ICSI defined as the appearance of 2 pronuclei) Cycles with total fertilisation failure |
| Embryo data | Embryo quality (ie, good quality blastocysts according to Gardner classification) Embryo time-lapse kinetics including cleavage patterns Embryo utilisation rate (number of transferred + cryopreserved embryos per number of 2 PN zygotes) |
| Freeze      | Number of frozen blastocysts (time frame: up to 6 days after oocyte pick up (OPU)) |
| Pregnancy   | Positive pregnancy test (positive urine or serum hCG 11-21 days after embryo transfer) Multiple pregnancy (period: up to 12 weeks after embryo transfer). Number of intrauterine gestations Ongoing pregnancy per transfer (fetal heartbeat on ultrasound in gestational week 7–8) |
| Miscarriage | Pregnancy loss rate (period: up to 12 weeks after embryo transfer) Biochemical pregnancies (positive urine or serum hCG 11-21 days after embryo transfer without any clinical signs of intra- or extraterine pregnancy) Ectopic pregnancy/PUL |
| Birth/offspring | All live birth episodes (all live births from the study oocyte collection (including second and further live births) Preterm delivery (delivery at gestational week 22–36+6) Birth weight/weight for gestational age Congenital anomaly diagnosed at birth |

ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation; OPU, oocyte pick up; PN, pronuclei; PUL, pregnancy of unknown location.
to randomisation. Some couples/women may experience no fertilisation after either IVF or ICSI in the study. This risk is not considered higher compared with women who do not participate in the study. The study is registered with the National Institute of Health’s ClinicalTrials.gov.

DISCUSSION
Worldwide, the rate of treatment cycles where oocytes are fertilised with ICSI is increasing, also in patients without severe male factor infertility. Currently, there is no evidence to support that ICSI results in a higher live birth rate compared with standard IVF in these patients. If the INVICSI study finds that ICSI is superior to standard IVF in cases without severe male factor infertility, the increase in use of ICSI is justified and may then be recommended. However, if the INVICSI study fails to show superiority of ICSI, standard IVF should be recommended as the preferred first choice method of fertilisation in patients without severe male factor infertility. This could potentially lead to significant cost savings and a higher use of standard IVF that is less invasive, closer to natural fertilisation and less expensive.

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Contributors SB and NLCF were responsible for the conception, design and execution of the study protocol. SB, NLCF and AP contributed to the initial revision and editing of the manuscript. AZ was consulted concerning the laboratory details of the study design. SB, NLCF, AP, AZ, ALM, UBK, MRPP, LFA, BN, HSN, LP and MLG contributed to the critical revision of the manuscript as well as the approval of the final version for submission in BMJ Open.

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REFERENCES
1. Palermo G, Joris H, Devroey P, et al. Pregnancies after intracytoplasmic injection of single spermatozoan into an oocyte. Lancet 1992;340:17–19.
2. de Geyter C, Calhaz-Jorge C, Kupka MS. A new technique for intracytoplasmic sperm injection: results from European registries. Hum Reprod Update 2020;26:200–15.
3. de Mouzon J, Chambers GM, Zegers-Hochschild F, et al. International Committee for Monitoring Assisted Reproductive Technologies. World report: assisted reproductive technology 2012. Hum Reprod 2020;35:1900–13.
4. Zagradinov P, Hsu A, Stern JE, et al. Temporal differences in utilization of intracytoplasmic sperm injection among U.S. regions. Obstet Gynecol 2018;132:310–20.
5. Boulet SL, Mehta A, Kissin DM, et al. Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection. JAMA 2015;313:255–63.
6. Evers JLHH, Santa Claus in the fertility clinic. Hum Reprod 2016;31:1381–2.
7. Tannus S, Son W-Y, Gilman A, et al. The role of intracytoplasmic sperm injection in non-male factor infertility in advanced maternal age. Hum Reprod 2017;32:119–24.
8. Gennarelli G, Caroso A, Canosa S, et al. ICSI versus conventional IVF in women aged 40 years or more and unexplained infertility: a retrospective evaluation of 685 cycles with propensity score model. J Clin Med 2019;8:1694.
9. Stfontournis IA, Kolibianakis EM, Lainas GT, et al. Live birth rates using conventional in vitro fertilization compared to intracytoplasmic sperm injection in bologna poor responders with a single oocyte retrieved. J Assist Reprod Genet 2015;32:691–7.
10. Li Z, Wang AY, Bowman M, et al. ICSI does not increase the cumulative live birth rate in non-male factor infertility. Hum Reprod 2018;33:1322–30.
11. Hoong SC, Fleetham JA, O’Keane JA, et al. A prospective randomized trial of conventional in vitro fertilization versus intracytoplasmic sperm injection in unexplained infertility. J Assist Reprod Genet 2006;23:137–40.
12. Practice committees of the American Society for Reproductive M, the Society for assisted reproductive technology. Electronic address aao. Intracytoplasmic sperm injection (ICSI) for non-male factor indications: a committee opinion. Fertil Steril 2020;114:239–45.
13. Johnson LNC, Sasson IE, Sammel MD, et al. Does intracytoplasmic sperm injection improve the fertilization rate and decrease the total fertilization failure rate in couples with well-defined unexplained infertility? A systematic review and meta-analysis. Fertil Steril 2013;100:704–11.
14. Vittek WS, Galarraga O, Klatsky PC, et al. Management of the first in vitro fertilization cycle for unexplained infertility: a cost-effectiveness analysis of split in vitro fertilization-intracytoplasmic sperm injection. Fertil Steril 2013;100:1381–8.
Kim HH, Bundorf MK, Behr B, et al. Use and outcomes of intracytoplasmic sperm injection for non-male factor infertility. *Fertil Steril* 2007;88:622–8.

Bhattacharya S, Hamilton MP, Shaaban M, et al. Conventional in-vitro fertilisation versus intracytoplasmic sperm injection for the treatment of non-male-factor infertility: a randomised controlled trial. *Lancet* 2001;357:2075–9.

Ruiz A, Remohi J, Minguez Y, et al. The role of in vitro fertilization and intracytoplasmic sperm injection in couples with unexplained infertility after failed intrauterine insemination. *Fertil Steril* 1997;68:171–3.

Isikoglu M, Avci A, Kendirci Ceviren A, et al. Conventional IVF revisited: is ICSI better for non-male factor infertility? randomized controlled double blind study. *J Gynecol Obstet Hum Reprod* 2020;50:101990.

van Rumste MME, Evers JLH, Farquhar CM. Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in patients with non-male subfertility. *Cochrane Database Syst Rev* 2003;2:CD001301.

Butts SF, Owen C, Mainigi M, et al. Assisted hatching and intracytoplasmic sperm injection are not associated with improved outcomes in assisted reproduction cycles for diminished ovarian reserve: an analysis of cycles in the United States from 2004 to 2011. *Fertil Steril* 2014;102:1041–7.

Luna M, Bigelow C, Duke M, et al. Should ICSI be recommended routinely in patients with four or fewer oocytes retrieved? *J Assist Reprod Genet* 2011;28:911–5.

van der Wasterlaken L, Helmerhorst F, Dieben S, et al. Intracytoplasmic sperm injection as a treatment for unexplained total fertilization failure or low fertilization after conventional in vitro fertilization. *Fertil Steril* 2005;83:612–7.

Chan A-W, Tetzlaff JM, Gotzsche PC, et al. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.

Kohn TP, Kohn JR, Ramasamy R. Effect of sperm morphology on pregnancy success via intrauterine insemination: a systematic review and meta-analysis. *J Urol* 2018;199:812–22.

Kohn TP, Kohn JR, Lamb DJ. Role of sperm morphology in deciding between various assisted reproduction technologies. *Eur Urol Focus* 2018;4:311–3.

Lemmens L, Kos S, Beijer C, et al. Predictive value of sperm morphology and progressively motile sperm count for pregnancy outcomes in intrauterine insemination. *Fertil Steril* 2016;105:1462–8.

Deveneau NE, Sinno O, Krause M, et al. Impact of sperm morphology on the likelihood of pregnancy after intrauterine insemination. *Fertil Steril* 2014;102:1584–90.

Hotaling JM, Smith JF, Rosen M, et al. The relationship between isolated teratozoospermia and clinical pregnancy after in vitro fertilization with or without intracytoplasmic sperm injection: a systematic review and meta-analysis. *Fertil Steril* 2011;95:1141–5.

Sha T, Wang X, Cheng W, et al. A meta-analysis of pregnancy-related outcomes and complications in women with polycystic ovary syndrome undergoing IVF. *Reprod Biomed Online* 2019;39:281–93.

Sigala J, Sifer C, Dewailly D, et al. Is polycystic ovarian morphology related to a poor oocyte quality after controlled ovarian hyperstimulation for intracytoplasmic sperm injection? results from a prospective, comparative study. *Fertil Steril* 2015;103:112–8.

Heijnen EMEW, Eijkemans MJC, Hughes EG, et al. A meta-analysis of outcomes of conventional IVF in women with polycystic ovary syndrome. *Hum Reprod Update* 2006;12:13–21.

Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.