HELDA
HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

UNIVERSITY OF HELSINKI

https://helda.helsinki.fi

Obstetric and perinatal risks after the use of donor sperm : A systematic review and meta-analysis

Pohjonen, E. M.

2022-07

Pohjonen , E M , Söderström-Anttila , V , Bergh , C , Loft , A , Magnusson , A , Pinborg , A , Oldereid , N B , Petzold , M , Romundstad , L B & Laivuori , H 2022 , ' Obstetric and perinatal risks after the use of donor sperm : A systematic review and meta-analysis ' , European Journal of Obstetrics, and Gynecology ,and Reproductive Biology , vol. 274 , pp. 210-228 . https://doi.org/10.1016/j.ejogrb.2022.05.031

http://hdl.handle.net/10138/346465
https://doi.org/10.1016/j.ejogrb.2022.05.031

cc_by
publishedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

European Journal of Obstetrics and Gynecology 274 (2022) 210–228

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Review article

Obstetric and perinatal risks after the use of donor sperm: A systematic review and meta-analysis

E.-M. Pohjonen [a,*], V. Söderström-Anttila [b], C. Bergh [c], A. Loft [d], Å. Magnusson [e], A. Pinborg [f], N.B. Oldereid [g], M. Petzold [h], L.B. Romundstad [i,j], H. Laivuori [a,k,l]

[a] Department of Obstetrics and Gynaecology, Tampere University Hospital, Tampere, Finland
[b] University of Helsinki, Helsinki, Finland
[c] Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University and Sahlgrenska University Hospital, Gothenburg, Sweden
[d] Fertility Clinic, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[e] Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska University Hospital, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden
[f] Fertility Clinic, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[g] Livio IVF-klinikken Oslo, Oslo, Norway
[h] School of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden
[i] Spiren Fertility Clinic, Trondheim, Norway
[j] Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway
[k] Faculty of Medicine and Health Technology, Center for Child, Adolescent, and Maternal Health Research, Tampere University, Tampere, Finland
[l] Institute for Molecular Medicine Finland (FIMM), Helsinki Institute of Life Science, University of Helsinki, Helsinki, Finland

ARTICLE INFO

Keywords:
Donor insemination
Donor sperm
Preeclampsia
Hypertensive disorders of pregnancy
Perinatal outcome

ABSTRACT

Donor sperm is widely used in infertility treatments. The purpose of the study was to investigate, whether use of donor sperm in intrauterine insemination (IUI) or in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatments affect maternal and perinatal risks compared with spontaneously conceived pregnancies or use of partner sperm in IUI, IVF or ICSI. We provide a systematic review and meta-analyses on the most clinically relevant obstetric and perinatal outcomes after use of donor sperm compared with partner sperm: hypertensive disorders of pregnancy, preeclampsia, low birth weight, and preterm birth. Our meta-analyses showed an increased risk for preeclampsia (pooled adjusted odds ratio (aOR) 1.77, 95% CI 1.26–2.48) and hypertensive disorders of pregnancy (pooled aOR 1.55, 95%, CI 1.20–2.00) in pregnancies resulting from IUI with donor sperm compared with IUI with partner sperm. No increased risk was seen for low birth weight or preterm birth after the use of donor sperm in IUI compared with the use of partner sperm in IUI. Subgroup analysis for singletons only did not change these results. The meta-analysis on low birth weight showed a lower risk after in IVF with donor sperm compared with IVF with partner sperm (pooled aOR 0.89, 95% CI 0.83–0.94). For hypertensive disorders of pregnancy, preeclampsia and preterm birth, no difference was found between IVF with donor sperm vs. partner sperm. Patients need to be informed about the moderately increased risk of hypertensive disorders of pregnancy and preeclampsia in pregnancies after IUI with donor sperm.

Abbreviations: IUI, intrauterine insemination; IUI-D, intrauterine insemination with donor sperm; IUI-H, intrauterine insemination with partner sperm; IVF, in vitro fertilization; IVF-D, IVF treatment using donor sperm; IVF-H, IVF treatment using partner sperm; ICSI-D, intracytoplasmic sperm injection with donor sperm; ICSI-H, intracytoplasmic sperm injection with partner sperm; SC, spontaneously conceived; PE, preeclampsia; HDP, hypertensive disorders of pregnancy; PIH, pregnancy-induced hypertension; OS, ovarian stimulation; aOR, adjusted odds ratio; aRR, adjusted risk ratio LBW, low birth weight; VLBW, very low birth weight; HBW, high birth weight; SGA, small for gestational age; LGA, large for gestational age; PTB, preterm birth; M/F ratio, male to female ratio, sex ratio.

* Corresponding author at: Tampereen yliopistollinen sairaala. Elämänaukio 2, 33520 Tampere, Finland.
E-mail address: eeva-maria.pohjonen@tuni.fi (E.-M. Pohjonen).

https://doi.org/10.1016/j.ejogrb.2022.05.031
Received 26 January 2022; Received in revised form 24 May 2022; Accepted 25 May 2022
Available online 30 May 2022
0301-2115/© 2022 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

Intrauterine insemination with donor sperm (IUI-D) became widely used and socially acceptable in the mid part of the 20th century, although the first IUI-D took place already in 1884 [1]. In the 1990́s, after the intracytoplasmic sperm injection (ICSI) technique was introduced, a growing proportion of men had a chance of producing offspring, if at least some spermatozoa were available for treatment. Still, in some cases, treatment using donor sperm is the only alternative for severe male factor infertility. New and growing patient groups for IUI-D are same sex female couples and single women seeking infertility treatment [2–5]. Unlike couples with infertility, these women are usually fertile and have good reproductive health [3]. The trend for all patient groups is delayed parenthood (to an older age)[6]. This inevitably leads to increased maternal risks in pregnancy because of the age factor per se [7–9] and because of underlying chronic diseases, such as chronic hypertension [10]. In vitro fertilization (IVF) using donor sperm (IVF-D) is a treatment option for couples with male factor infertility when IUI-D treatment fails, or when there is a female factor present, e.g. a tubal factor, severe endometriosis, or increased age of the woman.

Over the years, increasing evidence of a higher risk of preeclampsia (PE) in pregnancies after use of donor sperm has arisen [11–14]. Hypertensive disorders of pregnancy (HDP) and PE are not only associated with adverse maternal and fetal short-term outcomes [15] but also with increased morbidity and mortality in later life of the mother [16] and the child [17]. Interestingly, a recent study on adults born after conception with donor sperm reported poorer long-term health outcomes (diabetes, thyroid disease, environmental allergies and sleep apnoea) [18].

Objectives and rationale

Systematic reviews on the use of donor sperm and obstetric and perinatal outcomes are scarce [11,19–21]. Most earlier studies have compared IUI-D pregnancies with use of partner sperm in IUI (IUI-H) or spontaneously conceived (SC) pregnancies, and only a few studies have reported data on IVF-D pregnancies compared with use of partner sperm in IVF (IVF-H). Additionally, the study populations have changed over time compared with earlier decades because of increasing childbearing age [5,22,23] and consequently increasing risks for morbidity among these women. Moreover, the use of donor sperm is increasing, due to use for same sex female couples and single women.

This systematic review and meta-analysis aim to assess the risk of HDP and, PE, as well as perinatal outcomes in both IUI-D and IVF-D cycles compared with IUI-H, IVF/ICSI-H and SC pregnancies.

Methods

We used the Prisma Statement guideline checklist for systematic reviews (Prisma guidelines). Eligibility criteria were: English language, publication date 1946 - December 2020. The last literature search was performed on December 18, 2020. Systematic reviews with meta-analyses, randomized controlled trials (RCTs) and non-randomized cohort studies were included. All studies with suitable control groups were included without limiting cohort size. Studies published only as abstracts, case series as well as systematic reviews without meta-analyses were excluded (Table S1).

We searched Ovid Medline, Ovid EBM (incl. Cochrane), Scopus, Web of Science, and Pubmed (Medline) for medical subject headings (MeSH-terms) as well as text words related to use of donor sperm in different types of infertility treatments (IUI or IVF or ICSI) and obstetric and perinatal complications (Supplementary Fig. S1). The main outcomes were HDP (including PE, gestational hypertension or pregnancy induced hypertension (PIH)), low birth weight (LBW, defined as birth weight < 2500 g), preterm birth (PTB, defined as birth before 37 gestational weeks + 0 days), fetal sex ratio and birth defects. Several studies reported gestational hypertension as PIH. Screening by reading abstracts was carried out by three authors (E.-M.P., V.S.-A. and H.L.). Every record was screened by at least two authors, the majority was screened by all three. We excluded studies that had pooled different treatment modalities in one cohort group, for example IUI-D and IVF-D taken together and compared with IVF-D. Studies on double donation, i.e. donation of both oocytes and sperm were also excluded, to avoid bias from the obstetric and perinatal risks in oocyte donation [24] (Supplementary Table S1).

Data collection was performed with pre-designed, structured tables by E.-M.P, V.S.-A. and H.L. Quality assessment was carried out with a grading system for precision and directness and with Robins-I tool [25] for the risk of bias (Supplementary Table S2). All quality assessments were carried out by at least two authors (E.-M.P, V.S.-A. and H.L.).

Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used for evaluating certainty of evidence [26]. The GRADE system evaluates study design, limitations, consistency, directness, precision, publication bias and effect. Certainty levels were high, moderate, low, very low. Certainty levels correlated with how confident evaluators are on the effect estimates of studies. Adjusted odds ratios (aORs) and adjusted risk ratios (aRRs) were used if they were reported in the included studies. Adjustments are specified in the outcome tables, but as adjustments differ between studies, the RRs are not directly comparable. If studies did not report ORs/RRs, they were calculated prior to meta-analyses, when sufficient data for this could be collected (e.g. case numbers, size of groups). If this was not possible, studies were left out from the meta-analyses, but included in the text.

We conducted meta-analyses on four key outcomes: PE, HDP, LBW, and PTB. Separate analyses were made comparing IUI-D with either IUI-H or SC pregnancies as well as IVF-D with IVF-H. We conducted separate meta-analyses for studies presenting singleton data, and studies presenting data for the whole treatment population, including multiple pregnancies. For all the meta-analyses, a random effect model was applied using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model. Stata 17.0 software was used.

Results

After duplicates were removed, 1928 records were eligible for screening (Fig. 1 Prisma flow chart). Altogether, 72 full-text articles were assessed and after exclusion, 24 were included in qualitative synthesis (Table 1). No RCTs were identified.

Hypertensive disorders of pregnancy

We included ten original studies and two systematic reviews on hypertensive outcomes after use of donor sperm with results outlined in Table 2. Quality assessment of the included studies is shown in Supplementary Table S2. Nine out of 10 studies were assessed having low or moderate risk of bias. These studies were adjusting for factors such as maternal age, parity, number of fetuses, pre-existing hypertension, and gestational diabetes.

Earlier systematic reviews and meta-analyses

In a systematic review, Gonzalez-Comadran et al. (2014) reported an increased risk of PE (OR 1.63, 95%CI 1.36–1.95) but not of gestational hypertension in the donor sperm pregnancies compared with those of partner sperm [19]. However, IUI-D/IVF-D pregnancies were pooled in the study group and IUI-H/IVF-H pregnancies in the control group. A recent meta-analysis reported an increase of PE (RR 1.49; 95 % CI 1.05–2.09) and HDP (RR 1.44; 95 % CI 1.17–1.78) after use of donor sperm compared with partner sperm, however also after pooling IUI-D and IVF-D pregnancies in the study group and IUI-H and IVF-H pregnancies in the control group [11]. In a subgroup analysis for IUI-D vs IUI-H, the increased risk for HDP persisted (RR 1.42, 95%CI 1.09–1.84) [11] (Table 2).

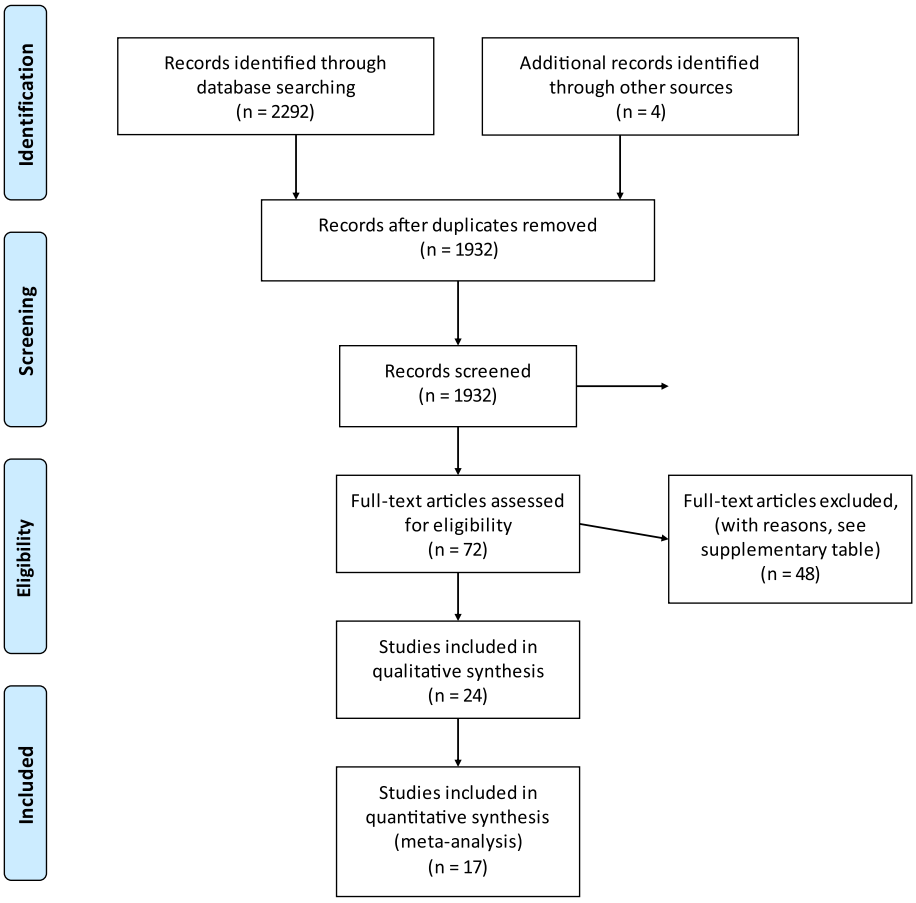

Fig. 1. Prisma flow chart.

IUI-D vs IUI-H

Three studies were included in our meta-analysis on PE, and four studies in the meta-analysis for HDP. The risk for PE was significantly higher in IUI-D vs IUI-H, (pooled OR 1.77, 95% CI 1.26–2.48) (Fig. 2a). The risk for HDP was also increased in IUI-D compared with IUI-H, (pooled OR 1.55, 95% CI 1.20–2.00) (Fig. 3a). The risk of bias was low in two studies and moderate in two studies. The number of included patients in the individual studies ranged from 29 to 1881. One study included singletons only while the other three adjusted for singletons, which however did not change the results (Supplementary Fig. S2,4).

IUI-D vs SC pregnancies

Two studies were included in the meta-analysis on PE, and five studies in the meta-analysis on HDP comparing IUI-D and SC pregnancies. After IUI-D there was an increased risk for PE (pooled OR 1.40, 95% CI 1.15–1.71) (Fig. 2b) as well as for HDP (pooled OR 1.56, 95% CI 1.29–1.88) (Fig. 3b) compared with SC pregnancies. The risk of bias was low in two studies, moderate in two studies, and serious in one study. The number of patients in the IUI-D group in the studies varied from 35 to 1881. Data on singletons were provided in three studies, one study adjusted for singletons and one study did not adjust, and stated, that the IUI-D group had more multiple pregnancies (Table 2). Our meta-analysis on HDP with studies providing singleton data or with adjustment for singletons showed an increased risk in the IUI-D group (pooled OR 1.63, 95%CI 1.20–2.20) (Supplementary Fig. 5).

IVF/ICSI-D vs IVF/ICSI-H

Two large register studies were included in the meta-analysis for HDP (Fig. 3c). No increased risk for HDP after IVF-D treatment was seen (pooled OR 1.05, 95%CI 0.78 – 1.40). The risk of bias was moderate in both studies. Both studies included only singletons and adjusted for numerous confounding factors. Furthermore, Kennedy et al. (2019) reported no increased risk for HDP in multigravidas using sperm from a new donor (aOR 1.18; 95% CI: 0.69–2.04) [27]. No studies providing PE data after IVF/ICSI-D were identified.

Conclusions: IUI-D is probably associated with a moderately increased risk of PE and HDP, moderate certainty of evidence (GRADE ⊕⊕⊕O).

There may be little or no difference in the risk of HDP between IVF/ICSI-D and IVF/ICSI-H, low certainty of evidence (GRADE ⊕⊕OO).

Perinatal outcomes

We included 18 original studies and two systematic reviews reporting on perinatal outcomes after the use of donor sperm. Among these studies, 11 compared IUI-D with either IUI-H or SC pregnancies. Seven studies compared IVF-D with IVF-H (Table 1). Twelve of 18 studies reporting perinatal outcomes were assessed having low to moderate risk of bias. The others were assessed having either a serious risk of bias or other shortcomings in quality, e.g. low precision. In general, all the large register studies had adequate sample sizes and included comparison groups, and the risk of bias was either low or moderate (Supplementary Table S2).

Earlier systematic reviews and meta-analyses

Three systematic reviews and meta-analyses were identified on donor sperm and perinatal outcomes [11,20,21].

Regarding LWB and IUI-D, Adams et al. (2017) found no increased risk in their meta-analyses of two studies [20]. However, after updating their meta-analysis with three additional studies, the risk of LBW was slightly increased between children born after IUI-D and those born after SC (RR 1.17, 95%CI 1.03–1.33) [21]. Allen et al. (2021) found an

Table 1
Included studies.

Author, year, country	Study design Population	Study duration (years)	Exposure	Patients (n)	Comment	Outcome variables
Systematic reviews						
Adams 2017 (update 2018), Australia	systematic review + meta-analysis	studies published before 2018	IUI-D vs SC /IUI-H	varied according to outcome, range 1638–5358 in IUI-D group, 8068 – 637 843 in SC/ IUI-H group		LBW, PTB, birth defects
Allen 2021, UK	systematic review + meta-analysis	studies published before 2019	IUI-D/ IVF/ ICSI-D vs IUI-H/ IVF/ ICSI-H/ SC	varied according to outcome, range 60 – 23 929 in IUI-D/IVF-D/ICSI-D group, 7668 – 5 229 762 in IUI-H/IVF-H/ICSI-H/ SC group		Hypertensive disorders, PE, PTB, BW, congenital anomaly, SGA, LGA, ectopic pregnancy, miscarriage, GDM, placental abruption, placenta praevia, stillbirth, neonatal death
Gonzales-Comadran 2014, Spain	systematic review + meta-analysis	studies published before 2014	IUI-D/ IVF/ ICSI-D vs IUI-H/ IVF/ ICSI-H/ SC	10 898 women (2342 IUI-D/ IVF/ICSI-D, 8556 IUI-H/ IVF/ ICSI-H)		PE and PIH
Donor insemination (IUI-D)						
Adams 2017, Australia	cohort, register study	1986–2002	IUI-D vs SC	476 IUI-D, 297 280 spontaneous conceptions, live births		LBW, gestational age, SGA, LGA
Chen 2018, China	cohort	2012–2015	IUI-D vs IUI-H	173 IUI-D pregnancies, 304 IUI-H pregnancies		Sex, gestational age, PTB, LBW, BW, birth defects
Davies, 2012 Australia	cohort, register study	1986–2004	IUI-D vs SC	428 IUI-D pregnancies, 302 811 SC pregnancies		Birth defects
Gaudoin 2003, Scotland	cohort	1993–1997	IUI-D vs IUI-H vs SC	35 IUI-D, 97 IUI-H, 109 311 (national cohort) births		LBW, PTB, PE
Hoy 1999, Australia	cohort	1982–1995	IUI-D vs SC	1552 IUI-D, 7717 SC pregnancies		PE, sex, PTB, LBW, birth defects, PD
Huang 2016, China	cohort	2006–2012	IUI-D vs SC	1623 IUI-D-infants vs 1018 SC infants		Sex ratio, BW, multiple births, birth defects.
Kyrou 2010, Belgium	Cohort	1999–2006	IUI-D vs IUI-H	438 IUI-D, 275 IUI-H births		PE
Lansac 1997, France	cohort	1987–1994	IUI-D and IVF-D vs SC	18,128 IUI-D infants, 3405 IVF-D infants	Comparison of malformations to national register (13,631 children)	Malformations, LBW, PTB
Malchau 2014, Denmark	cohort (Danish national register)	2007–2012	IUI-D vs IUI-H, IVF, ICSI, SC	1881 singletons (IUI-D), 4228 singletons (IUI-H) 229 749 (SC)		PTB, LBW, SGA, LGA. Hypertensive disorders.
Salha 1999, UK	cohort		IUI-D vs IUI-H	33 IUI-D, 33 IUI-H		PE, PIH
Smith, 1997, Canada	cohort		IUI-D vs IUI-H	37 IUI-D, 44 IUI-H		PE
Varma 1987, UK	cohort (prospective)	1983–1985	IUI-D vs SC	72 (IUI-D), 7893 (SC) pregnancies		PIH, PTB, birth weight, malformations, sex ratio
Yan 2011 China	cohort (Birth defect register)	2004–2008	IUI-D vs IUI-H	1572 IUI-D infants, 873 IUI-H infants		Birth defects and anomalies
Zhou 2018, China	cohort	2013–2015	IUI-D vs IUI-H	1899 IUI-H deliveries vs 808 IUI-D deliveries (in a 3-year period).		PTB, post term in IUI group, birth defects
IVF using donor sperm (IVF-D)						
Castillo 2019, UK	cohort	1991–2015	IVF/ICSI-D vs IVF/ICSI-H	68 IVF/ICSI-D live singleton births, 2712 IVF/ICSI-H live singleton births		Birth weight, gestational age
Gerkowicz 2018, USA	cohort	2010–2014	IVF/ICSI-D vs IVF/ICSI-H	6318 IVF/ICSI-D live births, 134 592 IVF/ICSI-H live births		PTB, LBW
Kamath 2018, UK	cohort.	1999–2011	IVF/ICSI-D vs IVF/ICSI-H	4523 IVF/ICSI-D singleton live births, 91 264 IVF/ICSI-H singleton live birth		PTB, LBW, post-term birth
Kennedy 2019, Australia	cohort	2009–2017	IVF/ICSI- D vs IVF/ICSI-H	1435 IVF-ICSI-D vs 13 191 IVF-H/ICSI-H singleton births		PE, HDP, fetal growth restriction
Luke 2016, USA	cohort study, (MOSART) register study	2004–2008	IVF/ICSI-D vs IVF/ICSI-H	283 IVF/ICSI-D live births, 8948 IVF/ICSI-H live births		Pregnancy hypertension, gestational age, PTB, LBW, SGA, LGA, birth defects.
Thapar 2007, UK	cohort	before 2007	IVF-D vs IVF-H	170 IVF-D births, 378 IVF-H births		HDP, LBW
Yu 2018, USA	cohort, register study	2012–2013	IVF/ICSI-D vs IVF/ICSI-H	2123 IVF-D, 42 799 IVF-H, first cycles, fresh cycles		BW, PTB

IUI-D = intrauterine insemination with donor sperm (AID), IUI = intrauterine insemination with partner sperm (AIH), IVF-D = IVF treatment using donor sperm, IVF-H = IVF treatment using partner sperm, ICSI = intracytoplasmic sperm injection, ET = embryo transfer, SC = spontaneously conceived pregnancies, GA = gestational age, SGA = small for gestational age, LGA = large for gestational age, PTB = preterm birth, BW = birth weight, LBW = low birth weight, VLBW = very low birth weight, HBW = high birth weight, VHBW = very high birth weight, M/F ratio = male to female ratio, gender ratio, PE = preeclampsia, PIH = pregnancy-induced hypertension, HDP = hypertensive disorders in pregnancy, GDM = gestational diabetes mellitus, BMI = body mass index, ToP = termination of pregnancy.

Table 2
Outcomes: hypertension.

Author, year, country	Study design	Cases	Outcomes (risk estimates)	Reference group	Adjustments, comments	Risk of bias	Directness	Precision
Hypertensive disorders Systematic reviews and meta-analyses n = 2								
Gonzalez-Comadran Spain, 2014	systematic review and meta-analysis	Pre-eclampsia: 212 Gestational hypertension: 11	Primary outcome preeclampsia: OR 1.63 (95% CI 1.36–1.95) Secondary outcome gestational hypertension: OR 0.94 (95% CI 0.43–2.03)	IUI-H, IVF/ICSI-H and SC pregnancies in the same control group	7 studies in PE analysis 4 studies in gestational hypertension analysis			
Allen 2021, UK	Systematic review and meta-analysis	Combined hypertensive disorders: 456 PE: 211 PIH: 83	Meta-analysis including all treatment modalities: Combined HDP RR 1.44 (95% CI 1.17–1.78),PE RR 1.49 (95% CI 1.05–2.09),PIH RR 1.24 (95%CI 0.87–1.76) Subgroup meta-analysis comparing IUI-D vs IUI:PE RR 1.55 (95% CI 1.01–2.39) Subgroup meta-analysis comparing IUI-D vs SC:PE RR 1.62 (95%CI 1.35–1.96)	IUI-H, IVF/ICSI-H, SC pregnancies				
Hypertensive disorders Original articles n = 10 IUI-D vs IUI-H / spontaneously conceived pregnancies.								
Adams 2017, Australia	cohort n = 476 (SAPSC register study)	PIH 64	Occurrence of PIH (HDP) was significantly elevated among donor-conceived singleton deliveries. Data not shown in article but p = 0.007	neonates (live births and still births, SC pregnancies in general population)	Included multiple pregnancies. Subanalysis for singletons only	Low	Good	Good
Gaudoin 2003, Scotland	Cohort, n = 35	Case numbers not given	Preeclampsia: IUI-D: 8.6% SC: 6.2%OR 1.41 (95% CI 0.43 – 4.63)	SC pregnancies (national cohort)	All singletons, primigravida. Ovarian stimulation for all IUI-D patients	Moderate	Fair	Fair
Hoy 1999, Australia	cohort n = 1552	131	Preeclampsia: IUI-D: 8.4% SC: 5.2%aOR 1.4, (95% CI 1.2–1.8)	SC pregnancies (general population)	Included multiple pregnancies. Adjusted for maternal age, parity, multiple birth, presentation	Moderate	Good	Good
Kyrou 2010, Belgium	cohort n = 438	48	Preeclampsia: IUI-D: 10.9% IUI-H: 7.2%difference 3.7%, (95% CI −0.8–7.8)	IUI-H pregnancies	multiple pregnancies included. Primary infertility, no known medical disorders, age < 40 years Adjusting for type of sperm, cycle number, number of babies	Moderate	Good	Good
Malchau 2014, Denmark	national cohort study n = 1881	140	Hypertensive disorders IUI-D: 7.4% SC: 3.7%7.4 % vs 3.7%, p < 0.001	IUI-H and SC pregnancies	All singletons	Low	Good	Good
Salha 1999, UK	cohort n = 33	All hypertensive 9 PE 6 PIH 3 Singletons only: All hypertensive 7 PE 4 PIH 3	Hypertension: IUI-D: 27,3% IUI-H: 3% p < 0.05 Preeclampsia: IUI-D: 18,2% IUI-H: 0% p < 0.05 Pregnancy-induced hypertension 9.1% vs 3% Adjusted for singletons only: Pre-eclampsia: 13.8% vs 0%, Pregnancy-induced hypertension: 10.3% vs 3.7%	IUI-H pregnancies	Included multiple pregnancies. control group (IUI) received OS with FSH vs IUI-D (natural cycle). More multiples in IUI group. Groups matched for age, parity, demographic background. Further adjustment for number of babies at delivery.	Moderate	Fair	Fair

(*continued on next page*)

Table 2 (*continued*)

Author, year, country	Study design	Cases	Outcomes (risk estimates)	Reference group	Adjustments, comments	Risk of bias	Directness	Precision
Smith 1997, Canada	cohort n = 37	PE 9	Preeclampsia:IUI-D: 9/37 (4 mild, 5 severe of which 1 HELLP)IUI-H: 3/44 (all 3 mild)RR 1.85 (95%CI 1.20–2.85)No difference in the number of inseminations among those who developed PE (p = 0.69)	IUI-H pregnancies	All cases: primary infertility, no known medical disorders. Included multiple pregnancies. Groups were comparable regarding maternal age, GA, BW, gender of fetus, twin pregnancies.	Low	Good	Fair
Varma 1987, UK	prospective cohort n = 60	7	Pregnancy-related hypertension: IUI-D: 11.7% SC: 12.5%OR 0.92 (95% CI 0.42 – 2.03)	SC pregnancies (general obstetric population + untreated infertility patients)	No adjustments. Both groups include multiple pregnancies.	Serious	Fair	Fair
IVF-D vs IVF								
Luke 2016, USA	cohort (MOSART study)	case numbers not reported	Pregnancy hypertension IVF/ICSI-D: 17.2% IVF/ICSI-H: 12.0%aOR 1.28 (95% CI 0.85–1.95)	singleton births with partner sperm treatment	Adjusted for maternal and paternal age, ethnicity, education, diagnoses, maternal preexisting medical conditions (hypertension, diabetes) plurality at 6 weeks, oocyte source, ICSI, AZH, embryo state and number of embryos transferred. Singleton data available.	Moderate	Good	Good
Kennedy 2019, Australia	cohort n = 1435	PE or PIH: 87 cases	All HDP: IVF/ICSI-D 6.1% IVF/ICSI-H: 5.2%aOR 0.94 (95% CI 0.73–1.21) Subanalysis of cohort including parity data aOR 1.31 (95% CI 0.90–1.90)	singleton births partner sperm treatment	All singletons. Adjusted for maternal age, BMI and ICSI. Subanalysis of cohort including parity data.	Moderate	Good	Good

IUI-D = intrauterine insemination with donor sperm (AID), IUI-H = intrauterine insemination with partner sperm (AIH), IVF-D = IVF treatment using donor sperm, IVF-H = IVF treatment using partner sperm, ICSI = intracytoplasmic sperm injection, SC = spontaneous conception, OS = ovarian stimulation, GA = gestational age, SGA = small for gestational age, LGA = large for gestational age, PTB = pre-term birth, BW = birth weight, LBW = low birth weight, VLBW = very low birth weight, HBW = high birth weight, VHBW = very high birth weight. M/F ratio = male to female ratio, PE = preeclampsia, PIH = pregnancy-induced hypertension, HDP = hypertensive disorders of pregnancy, GDM = gestational diabetes mellitus, BMI = body mass index. AZH = assisted hatching.
aOR = adjusted odds ratio. NS = no significant difference.

increased risk for small for gestational age (SGA) (RR 1.42, 95% CI 1.17–1.79), but no increased risk for LBW, very low BW (VLBW), high BW (HBW) or large for gestational age (LGA). The study population included both IUI-D and IVF-D patients and the control group included SC, IUI-H and IVF-H pregnancies. In a subgroup analysis a similar risk of SGA was observed comparing IUI-D to IUI-H or SC. When comparing IVF/ICSI-D with IVF/ICSI-H, there was a reduced risk of LBW and an increased risk of HBW in children born after donor pregnancies [11].

For the risk of PTB, the meta-analysis of Adams et al. (2017) showed no difference between children born after IUI-D or SC [20]. Allen et al. (2021) found no increased risk for PTB in their subgroup analyses comparing children born after IUI-D with IUI-H, or children born after IUI-D with SC or IVF/ICSI-D with IVF/ICSI-H [11].

Regarding the risk of birth defects, the updated meta-analysis by Adams et al. (2018) included five studies and reported an increased risk for birth defects in children born after use of donor sperm compared with children born after SC [21]. However, Allen et al. (2021) reported no increased risk for congenital anomalies in their meta-analysis including 11 studies [11].

The effect of donor sperm on low birth weight

IUI-D vs IUI-H

Two studies were included in the meta-analysis on LBW. The risk of LBW after IUI-D did not differ from that after IUI-H (pooled OR 0.46, 95% CI 0.07–3.28) (Fig. 4a). Both studies included singletons only. The risk of bias low in one, serious in one study. The study populations ranged from 173 to 1881.

Interestingly, the smaller study found children born after IUI-D to have higher BW compared with children born after IUI-H [28]. The difference was small, but statistically significant, although adjustment for some important confounding factors, such as maternal body mass index (BMI), parity, and smoking, were not considered (Table 3).

IUI-D vs SC pregnancies

Seven studies were included in the meta-analysis on LBW. The risk for LBW in children born after IUI-D did not differ from that after SC pregnancies (pooled OR 1.0, 95%CI 0.73–1.38) (Fig. 4b). Some of the studies provided data on singletons separately [29-32], whereas others included both singletons and multiples [12,33,34]. A meta-analysis on singleton only - data showed no increased risk for LWB (OR 1.01, 95%CI 0.80–1.71) in IUI-D vs. SC newborns (Supplementary Fig. S8). The risk of bias was low in two, moderate in two and serious in three studies. Cohort sizes varied from 35 to 8943 in IUI-D-treated patients (Tables 1, 3).

IVF/ICSI-D vs IVF/ICSI-H

Five studies were included in the meta-analysis of LBW comparing IVF/ICSI-D with IVF/ICSI-H (Fig. 4c).

Most studies comparing IVF/ICSI-D and IVF/ICSI-H were large

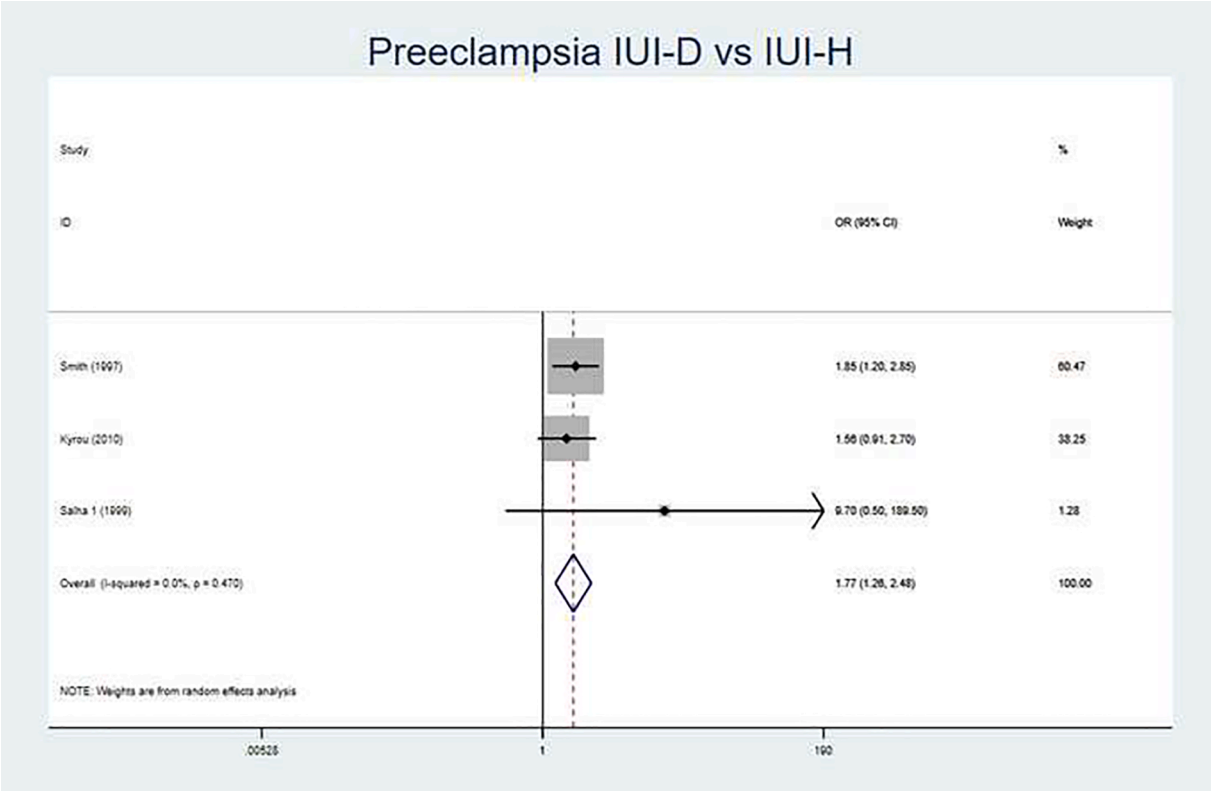

Fig. 2a. Meta-analysis PE, IUI-D vs IUI-H

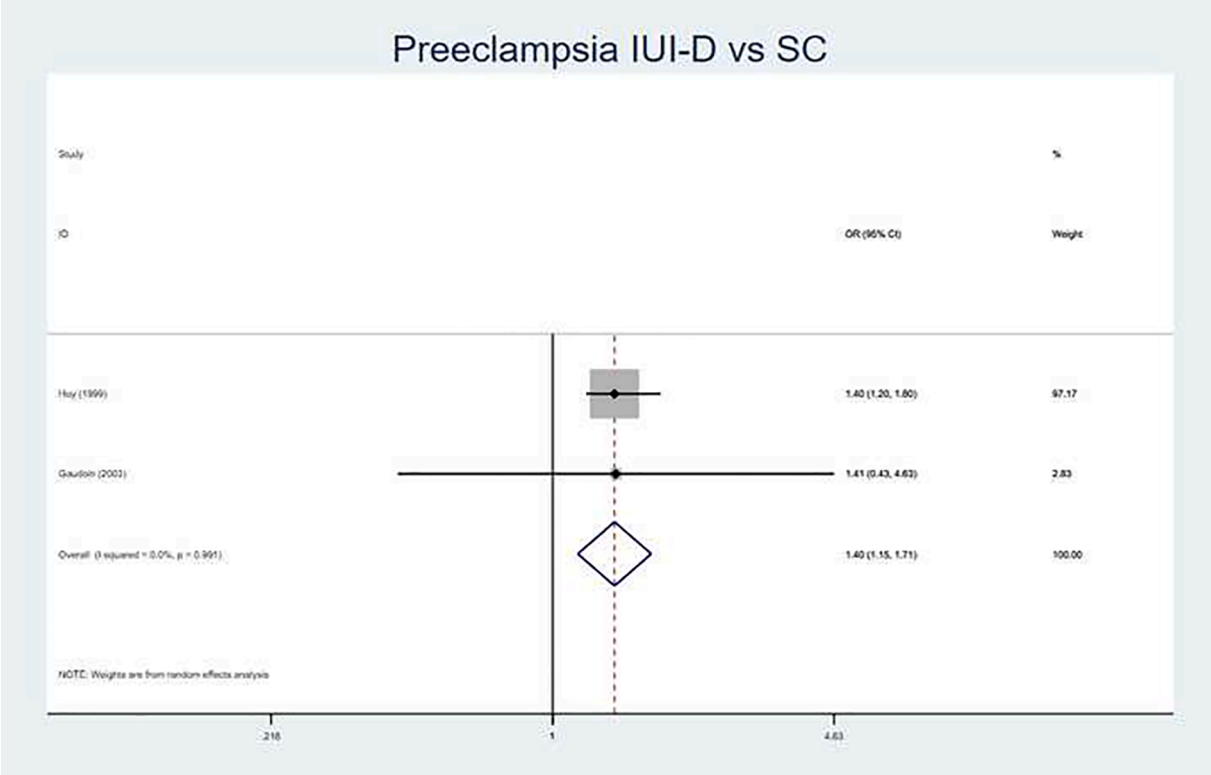

Fig. 2b. Meta-analysis PE, IUI-D vs SC.

register studies. The risk of bias was low or moderate in four studies and serious in one study.

The study populations ranged from 170 to over 6000 IVF-D pregnancies. All studies adjusted for singletons. The risk of LBW seems to be smaller for IVF/ICSI-D compared with children born after IVF/ICSI-H, pooled OR 0.89 (95% CI 0.83 – 0.94) (Fig. 4c). One study also

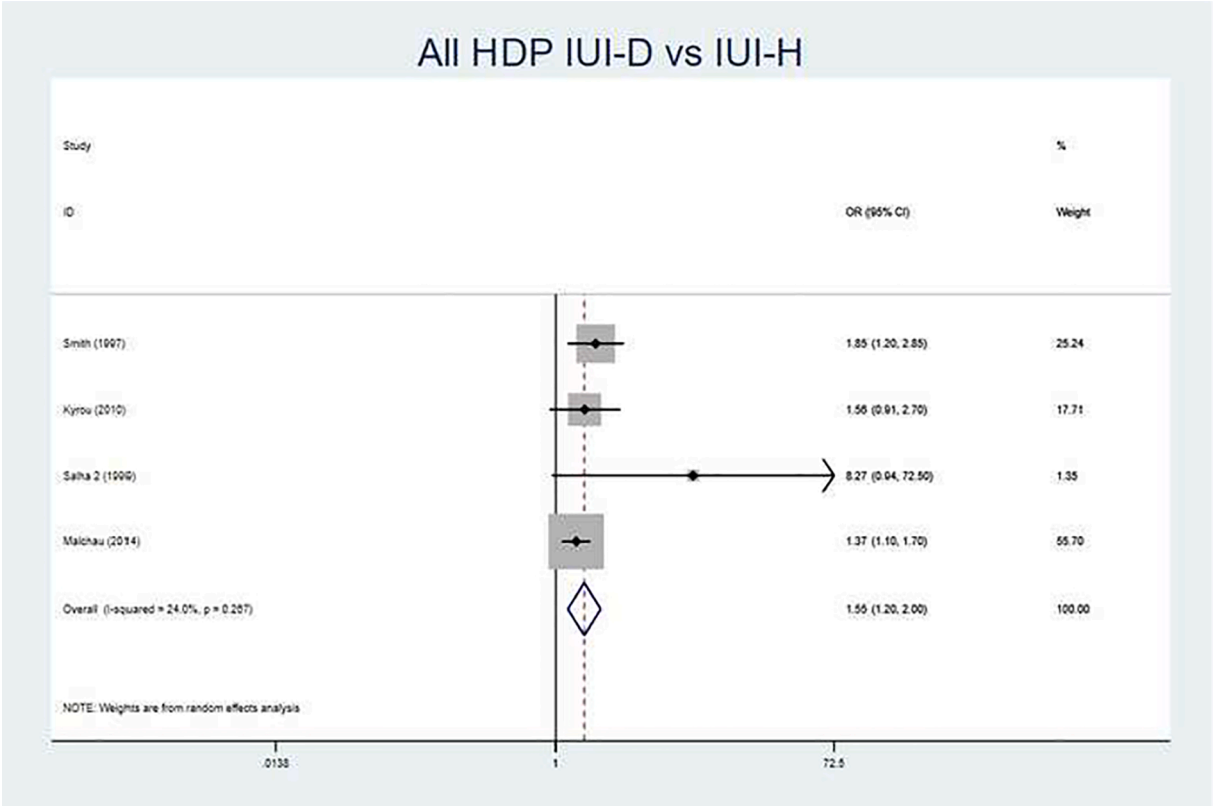

Fig. 3a. Meta-analysis, HDP, IUI-D vs IUI-H

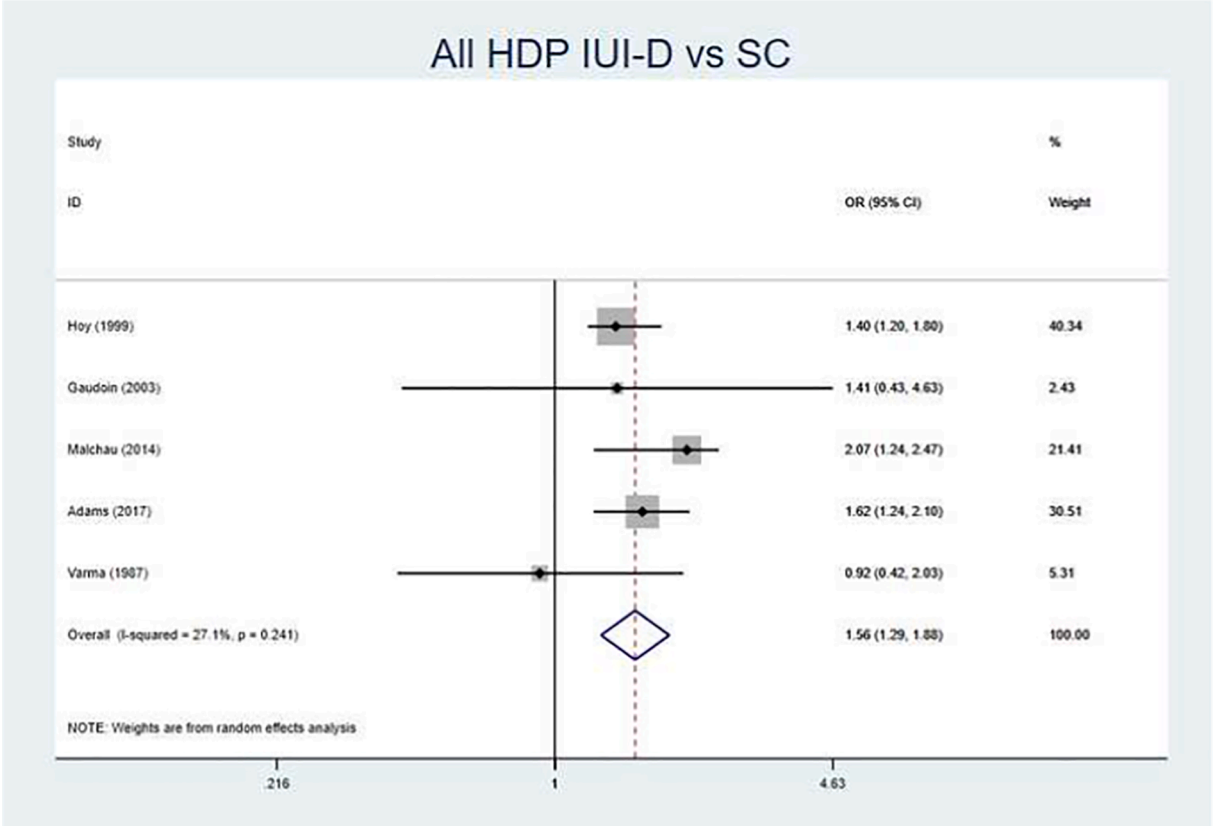

Fig. 3b. Meta-analysis HDP, IUI-D vs SC

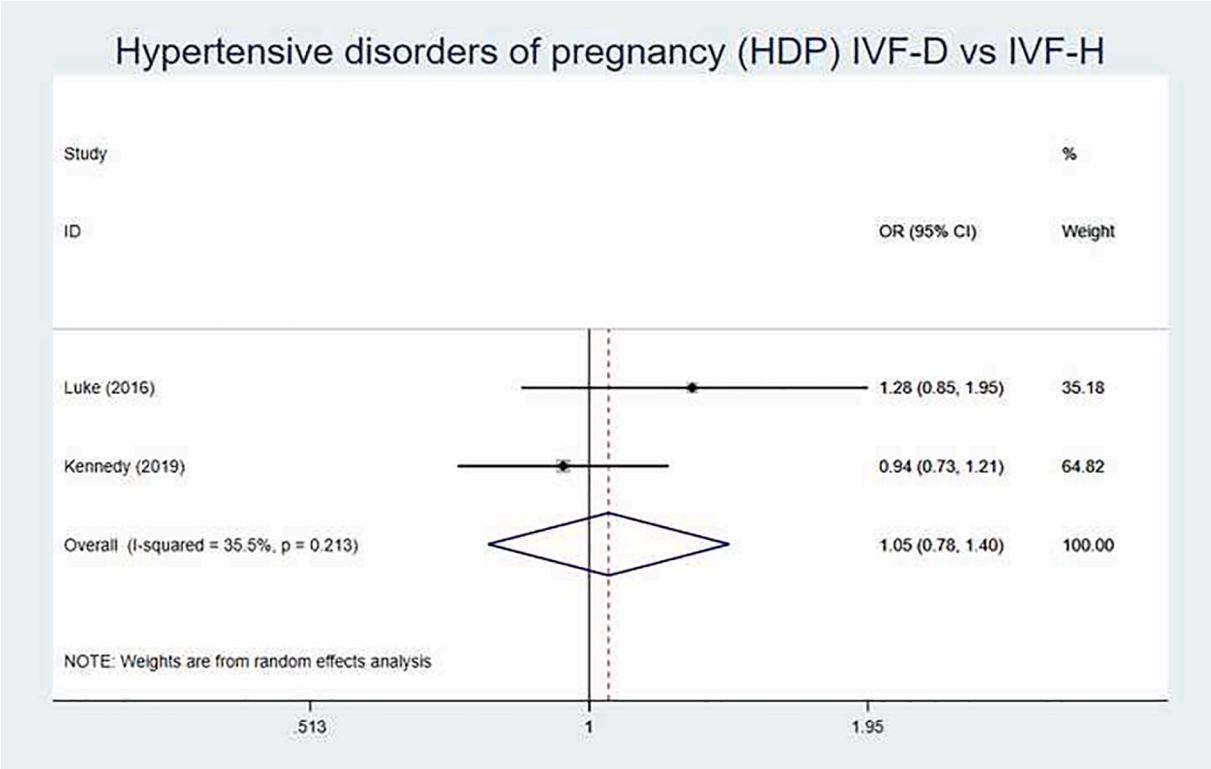

Fig. 3c. Meta-analysis HDP, IVF-D vs IVF-H.

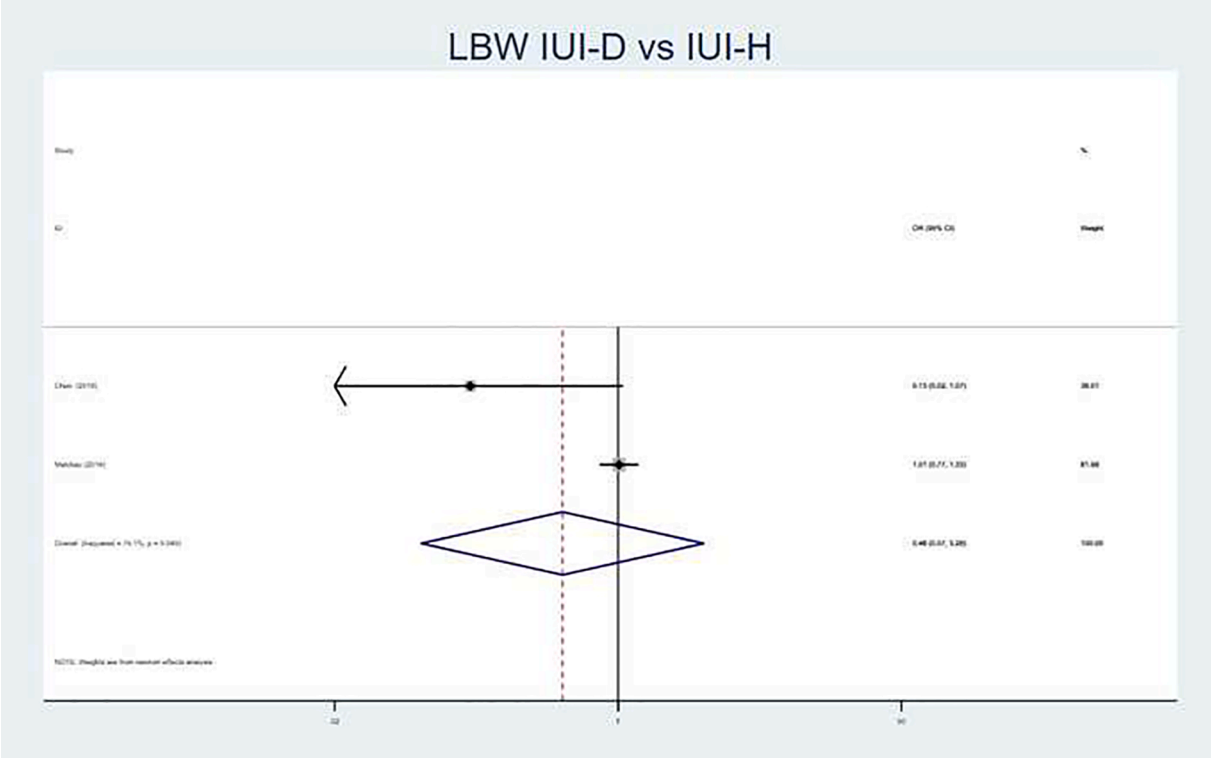

Fig. 4a. Meta-analysis LBW, IUI-D vs IUI-H

analyzed the risk of HBW, but no risk increase was seen [35]. Two studies which could not be included in the meta-analysis, also reported data on LBW in children born after IVF/ICSI-D [36,37] (Table 3). The results were consistent with our meta-analysis results.

Conclusion: There may be little or no difference in risk of LBW between children born after IUI-D and IUI-H, low certainty of evidence (GRADE ⊕⊕OO) or after IUI-D and SC pregnancies, low certainty of evidence (GRADE ⊕⊕OO). Use of IVF/ICSI-D may be associated with

Table 3
Outcomes: perinatal outcomes.

Author, year, country	Study design	Cases	Outcomes (risk estimates)	Reference group	Adjustments, comments	Risk of bias	Directness	Precision
Perinatal outcomes								
Systematic reviews and meta-analyses n = 2								
Adams 2017, Australia, updated 2018	Systematic review and meta-analysis	LBW < 2500 g: 259 PTB < 37w: 105 Birth defects: 93	Meta-analysis:LBW RR 1.17 (95%CI 1.03–1.33)PTB (<37 weeks)RR 1.05 (95%CI 0.91–1.21) NSBirth defects RR 1.30 (95%CI 1.05–1.59)	SC pregnancies	Original meta-analysis included 3 studies, updated meta-analysis included 6 studies. n = 1638–5358 depending on outcome.			
Allen 2021, UK	Systematic review and meta-analysis	SGA: 83 PTB: 1651 LBW: 1430 HBW: 574 LGA: 106 Birth defects: 173	Meta-analysis:SGA RR 1.42 (95% CI 1.15–1.76) (3 studies)PTB RR 0.98 (95% CI 0.88–1.08) NS (13 studies)LBW RR 0.97 (95%CI 0.82–1.15) NS (13 studies)HBW RR 1.28 (95%CI 0.94–1.73) NS (3 studies)LGA RR 1.01 (95%CI 0.84–1.22) NS (2 studies)Birth defects RR 1.15 (95%CI 0.86–1.53) NS (11 studies)	pregnancies conceived with partner sperm	Number of studies per outcome varied between 3 and 13. n = 2009–23743 depending on outcome			
Original articles n = 18								
IUI-D vs IUI-H / SC pregnancies								
Adams 2017, Australia	cohort (SAPSC register) n = 476	PTB: 24 LBW 22 PTB with LBW: 18 SGA: 40 LGA: 44	Singleton deliveries only: PTB: IUI-D: 5.5% SC: 5.5%OR 0.97 (95% CI 0.63–1.50) LBW: IUI-D: 5.1% SC: 4.7%OR 1.07 (95% CI 0.69–1.66) PTB with LBW: IUI-D: 4.2% SC: 3.0%OR 1.37 (95% CI 0.84–2.23) SGA IUI-D: 9.2% SC: 10.2%OR 0.84 (95% CI 0.59–1.20) LGA IUI-D: 10.2% SC: 9.9%OR 1.06 (95% CI 0.76–1.49)	neonates (live and stillborn spontaneous conception pregnancies in general population)	Population included multiple births. Singleton subanalysis. Adjustments for maternal age, parity, ethnicity, socio-economic background, fetal sex. Further adjustment: pre-existing hypertension, PIH, diabetes, GDM, epilepsy, asthma, anemia, did not produce change.	Low	Good	Good
Chen 2018, China	cohort n = 173	Birth defects: 1 LBW < 2500 g: 1 Preterm < 37w: 8	Fetal defects IUI-D: 0.6% IUI-H: 1.5% p = 0.753 Birth weight IUI-D: 3507 g IUI-H: 3384 g p = 0.020 LBW IUI-D 0.7% IUI-H 4.6%, p = 0.054 PTB IUI-D 5.2% IUI-H 8.4% p = 0.229 Gender ratio: IUI-D: 76/77 IUI-H: 122/140 p = 0.541	IUI-H pregnancies and live births	All singletons. Not adjusted for parity, smoking, BMI, ovarian stimulation. Groups were not comparable. Birth defect cohort includes clinical pregnancies and termination of pregnancy due to birth defect.	Serious	Poor	Fair

(*continued on next page*)

Table 3 (*continued*)

Author, year, country	Study design	Cases	Outcomes (risk estimates)	Reference group	Adjustments, comments			
Davies 2012, Australia	cohort, (SAPSC register) n = 428	36	Birth defects IUI-D: 8,4% SC: 5,7%aOR 1.37 (95% CI 0.98–1.92) NS	births from SC pregnancies, (fertile women with no prior ART)	Included multiple births. Singletons analyzed separately Adjustments:maternal age, parity, fetal sex, year of birth, ethnic group, maternal smoking and conditions in pregnancy (hypertension, diabetes, anemia, urinary infections) , socioeconomic status, occupation	Low	Good	Good
Gaudoin, 2003, Scotland	cohort n = 35	No case numbers given	LBW IUI-D vs SCOR 1.73 (95% CI 0.26–11.69) PTB: IUI-D: 5.7% SC: 6.9%	SC pregnancies in national cohort	All singletons, primigravid. OS used for all IUI-D: s Multivariate logistic regression analysis of factors associated with LBW performed	Moderate	Fair	Fair
Hoy 1999, Australia	cohort n = 1552	PTB < 37w: 103 LBW: 117 Birth defects: 57	PTB IUI-D: 6.4% SC: 6.6 %RR 1.0 (95% CI 0.8–1.2) LBW IUI-D: 7.3% SC: 6.8%RR 1.1 (95% CI 0.9–1.3) Birth defects IUI-D: 3.6% SC: 3.2 %RR 1.1 (95% CI 0.8–1.5) Sex ratio male infants IUI-D: 52.8% male infants SC: 51.2% RR 1.1 (95% CI 1.0–1.2)	SC pregnancies in general population	Included multiple births. No adjustments.	Moderate	Fair/good	Good
Huang 2016, China	cohort n = 1623	LBW < 2500 g: 28 Case numbers not given for all outcomes	Birth weight IUI-D: 3320 g SC: 3336 g p > 0.05 NS LBW IUI-D: 1.99% SC: 2.27% Macrosomia rate IUI-D: 8.18% SC: 4.89% p < 0,05 Preterm birth IUI-D: 3.2% SC: 1.87% p < 0.05 Birth defects: IUI-D: 1.42% SC: 0.29% (p < 0.01) Gender ratio similar to control group	SC infants	Included multiple births. Groups not comparable: High frequency of CS, more twins in IUI-D group	Serious	Poor	Good
Lansac 1997, France	cohort n = 16926 (IUI-D) and 2665 (IVF-D)	Birth defects: 325 (IUI-D)72 (IVF-D) LBW: 369 (IUI-D) Preterm birth: 429 (IUI-D)	Birth defectsIUI-D: 1.9% (rate similar compared to registers with SC) IVF-D: 2.74% IVF-H: 2.99% p = 0.16 NS LBW IUI-D 4.7% SC: 6.2% PTB IUI-D: 4.8% SC: 5.9%	SC births in general population. FIVNAT study data used as IVF comparison group (IVF with partner sperm)	Birth defect rates include pregnancy terminations Only live born singletons included in LBW and PTB data	Serious	Fair	Good
Malchau 2014, Denmark	national cohort register study n = 1881	LBW: 92 Preterm: 75 SGA: 72	LBW IUI-D 5.0% IUI-H: 4.9%aOR 1.014 (95% CI 0.775–1.326)	IUI-H, SC	All singletons. Adjustments for: Birth year, parity, maternal age, gender, BMI, smoking, cesarean	Low	Good	Good

(*continued on next page*)

Table 3 (*continued*)

Author, year, country	Study design	Cases	Outcomes (risk estimates)	Reference group	Adjustments, comments			
			PTB IUI-D: 4.0% IUI-H: 4.1%aOR 0.966 (95% CI 0.716–1.303) SGA IUI-D: 3.9% IUI-H: 3.8%aOR 0.992 (95% CI 0.736–1.337) LGA: IUI-D: 3.2% IUI-H: 2.8% LBW IUI-D: 5.0% SC: 3.4%,aOR 1.359 (95% CI 1.089–1.696) PTB IUI-D: 4.0% SC: 3.1%aOR 1.177 (95% CI 0.919–1.507) SGA IUI-D: 3.9% SC: 2.7%aOR 1.338 (95% CI 1.048–1.707)		section, induction of labor. Not adjusted for ovarian stimulation. Separate comparisons with IUI-H and SC pregnancies			
Varma 1987, UK	cohort n = 60–65 depending on outcome	LBW: 8 PTB: 2	LBW IUI-D: 12.3% SC: 11.5%OR 1.08 (95% CI 0.51 – 2.27) PTB IUI-D: 3.3% SC: 10%OR 0.012 (95% CI 0.0014–0.045)	general obstetric population (SC) and a small group of untreated infertility patients	Included multiples. No adjustments.	Serious	Fair	Fair
Zhou 2018, China	cohort n = 926	Birth defects (all clinical pregnancies): 11 Birth defects (live births only): 6 Preterm birth: 56	Birth defects within a 3-year period: IUI-D: 0.35–0.96% (of clinical pregnancies) IUI-H: 0.36–1.29% (of clinical pregnancies) (pergentages include pregnancy terminations) Birth defects:IUI-D: 6 (0.39–1.05% of LBs)IUI-H: 13 (0–1.52% of LBs)	IUI-H pregnancies and deliveries	No adjustments, no statistics between the groups. Includes all clinical pregnancies	Moderate	Moderate	Good
Yan 2011, China	cohort, register study n = 1572	Birth defects: 20	Birth defects IUI-D: 1.27 % IUI-H: 1.26 %	IUI-H births	No adjustments, no statistics between the groups	Serious	Moderate	Good
IVF-D/ICSI-D vs IVF/ICSI-H								
Castillo 2019, UK	cohort (HFEA register used partly) n = 68	case numbers not reported	Birth weight IVF/ICSI-D: adjusted BW in grams, linear regression model Beta 87.5 g (95% CI −62.8–237.9), p = 0.254	IVF-H singletons	Singletons. Adjusted for oocyte source, maternal parity, sex and gestational age	Moderate	Fair	Fair
Gerkowicz 2018, USA	cohort (CDC and NASS register) n = 6318	PTB 531 LBW 401	PTB: IVF/ICSI-D: 11.5% IVF/ICSI-H: 11.8%aRR 0.98 (95% CI 0.90–1.06) LBW IVF/ICSI-D: 8.8% IVF/ICSI-H: 9.4%aRR 0.91 (95% CI 0.83–0.99)	IVF/ICSI-H live births	PTB and LBW (singletons) adjusted for maternal age, gravidity, parity, number of cycles, diagnosis, stimulation type, hyperstimulation, number of oocytes, PGD/PGS. Subanalysis included BMI and smoking. LBR adjusted for maternal age	Low	Good	Good
Kamath 2018, UK	cohort (HFEA database) n = 4523	PTB < 37w: 398 Early PTB < 32w: 69 LBW < 2500 g: 377 VLBW < 1500 g: 77 HBW > 4000 g: 445	PTB: IVF/ICSI-D: 8.8% IVF/ICSI-H: 9.4%aOR 0.93 (95% CI 0.83–1.04) Early PTB IVF-ICSI-D: 1.5% IVF/ICSI-H: 1.8%aOR 0.86	IVF/ICSI-H live births	All singletons. Adjustments: age, duration of treatment, cause of infertility, previous live birth, number of embryos transferred.	Moderate	Good	Good

(*continued on next page*)

Table 3 (*continued*)

Author, year, country	Study design	Cases	Outcomes (risk estimates)	Reference group	Adjustments, comments			
		VHBW > 4500 g: 80 Post-term > 40w: 2238	(95% CI 0.67–1.11) LBW IVF/ICSI-D: 8.3% IVF/ICSI-H: 9.5%aOR 0.88 (95% CI 0.79–0.99) VLBW IVF/ICSI-D: 1.7% IVF/ICSI-H: 1.9%aOR 0.95 (95% CI 0.75–1.20) HBW IVF/ICSI-D: 9.8% IVF/ICSI-H: 8.8%aOR 1.09 (95% CI 0.98–1.21) VHBW IVF/ICSI-D: 1.8% IVF/ICSI-H: 1.5%aOR 1.15 (95% CI 0.90–1.45) Post-term birth IVF/ICSI-D: 49.5% IVF/ICSI-H: 47.0%aOR 1.10 (95% CI 1.03.1.17)					
Kennedy 2019, Australia	cohort n = 1435	Intrauterine growth restriction (estimated BW < 10th centile): 215	Fetal growth restriction IVF/ICSI-D: 15.2% IVF/ICSI-H: 18.1%aOR 0.85 (95%CI 0.72–1.0)	IVF/ICSI-H singleton live births	Adjustments: singletons, maternal age, BMI, fresh vs frozen cycle, day of embryo transfer.	Moderate	Good	Good
Luke, USA, 2016	MOSART register study n = 283	case numbers not reported	PTB: IVF/ICSI-D: 9.4% IVF/ICSI-H: 11.2%aOR 0.77 (95% CI 0.51–1.17) LBW IVF/ICSI-D: 5.9% IVF/ICSI-H: 8.1%aOR 0.63 (95% CI 0.39–1.01) SGA < 10th perc IVF/ICSI-D: 6.0% IVF/ICSI-H: 7.7%aOR 0.64 (95% CI 0.34–1.19) LGA > 95th perc: IVF/ICSI-D: 11.1% IVF/ICSI-H: 10.6%aOR 1.12 (95% CI 0.66–1.91) Birth defects: IVF/ICSI-D: 1.5% IVF/ICSI-H: 2.1%aOR 0.75 (95% CI 0.27–2.06)	IVF/ICSI-H singleton births	Adjusted for maternal and paternal age, ethnicity, education, diagnoses, maternal preexisting medical conditions (hypertension, diabetes) plurality at 6 weeks, oocyte source, ICSI, AZH, embryo state and number of embryos transferred.	Moderate	Good	Good
Thapar 2007, UK	cohort n = 170	LBW 10	LBW IVF-D:8.0 % IVF-H: 6.7%	IVF-H singleton births	Adjusted for singletons	Serious	Poor	Fair
Yu 2018, USA	cohort register study (SART CORS) n = 2123	PTB: 167 VPTB: 53 LBW: 127 VLBW: 21	PTB IVF/ICSI-D: 10.8% IVF/ICSI-H: 11.4%aEE 0.94 (0.78, 1.33) VPTB IVF/ICSI-D: 3.4% IVF/ICSI-H: 3.3%aEE 0.99 (0.73, 1.14) LBW IVF/ICSI-D: 8.4% IVF/ICSI-H: 9.0%aEE 0.87 (0.71, 1.06)	IVF/ICSI-H first treatment cycles	Singletons. Adjusted for maternal age, ethnicity, BMI, smoking, gravidity, history on PTB, FSH dose, blastocyst transfer, number of embryos transferred, cause of infertility Autologous oocytes only.	Moderate	Good	Good

(*continued on next page*)

Table 3 (*continued*)

Author, year, country	Study design	Cases	Outcomes (risk estimates)	Reference group	Adjustments, comments
			VLBW IVF/ICSI-D: 1.4% IVF/ICSI-H: 1.6%:aEE 0.82 (0.48, 1.39) NS Birth weight significantly lower in partner sperm group (3292 g +/- 601 vs 3233 g +/- 592 - (p = 0.003) adjusted effect estimate 42.8 g		

IUI-D = intrauterine insemination with donor sperm (AID). IUI = intrauterine insemination with partner sperm (AIH), IVF-D = IVF treatment using donor sperm, IVF-H = IVF treatment using partner sperm, ICSI = intracytoplasmic sperm injection, SC = spontaneously conceived pregnancy, GA = gestational age, SGA = small for gestational age, LGA = large for gestational age, PTB = preterm birth, BW = birth weight, LBW = low birth weight, VLBW = very low birth weight, HBW = high birth weight, VHBW = very high birth weight. M/F ratio = male to female ratio, sex ratio, PIH = pregnancy-induced hypertension, HDP = hypertensive disorders of pregnancy, PE = preeclampsia, GDM = gestational diabetes mellitus, BMI = body mass index. OD = oocyte donation, OS = ovarian stimulation, LBR = live birth rate. aOR = adjusted odds ratio. aEE = adjusted effect estimate, NS = not significant.

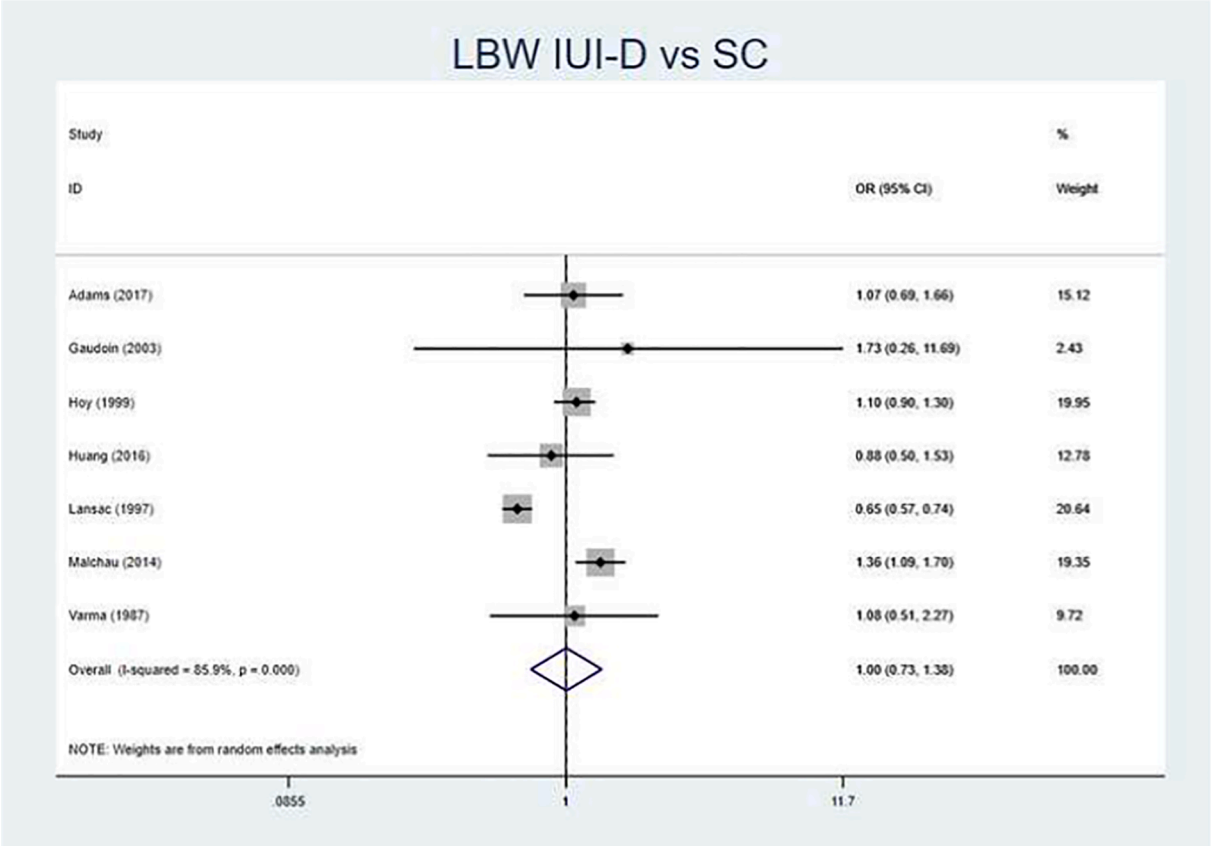

Fig. 4b. Meta-analysis LBW, IUI-D vs SC

slightly lower risk for children to be born with LBW compared to IVF/ICSI-H, low certainty of evidence (GRADE ⊕⊕OO).

The effect of donor sperm on preterm birth

IUI-D vs IUI-H

Three studies were included in the meta-analysis on PTB. Two of the three studies provided singleton data [28,31], and one included multiple pregnancies [38]. The risk for PTB after IUI-D did not differ from that of IUI-H (pooled OR 1.0, 95% CI 0.81–1.24) (Fig. 5a). A meta-analysis on only singletons showed no increased risk of PTB in IUI-D vs IUI-H (OR 0.90 95%CI 0.65–1.25) (Supplementary Fig. S7). According to Malchau et al. (2014) the risk of PTB in singletons born after IUI-D was 4.0%, compared to 4.1% in singletons born after IUI-H [31]. The risk of bias was low in one study, moderate in one study, and serious in one study. Size of the study population ranged from 173 to 1881.

IUI-D vs SC pregnancies

Six studies were included in the meta-analysis on PTB. The risk for PTB after IUI-D was not different from that of SC pregnancies (pooled OR

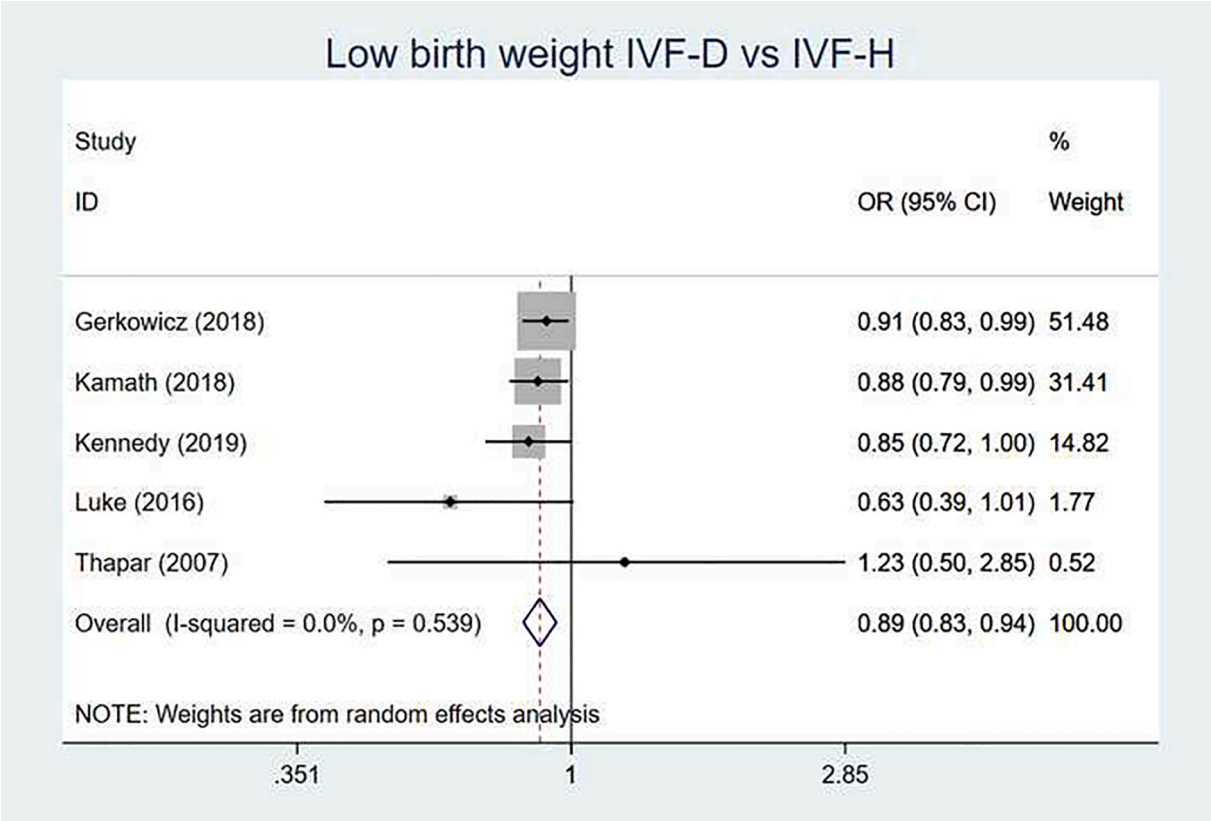

Fig. 4c. Meta-analysis LBW, IVF-D vs IVF-H.

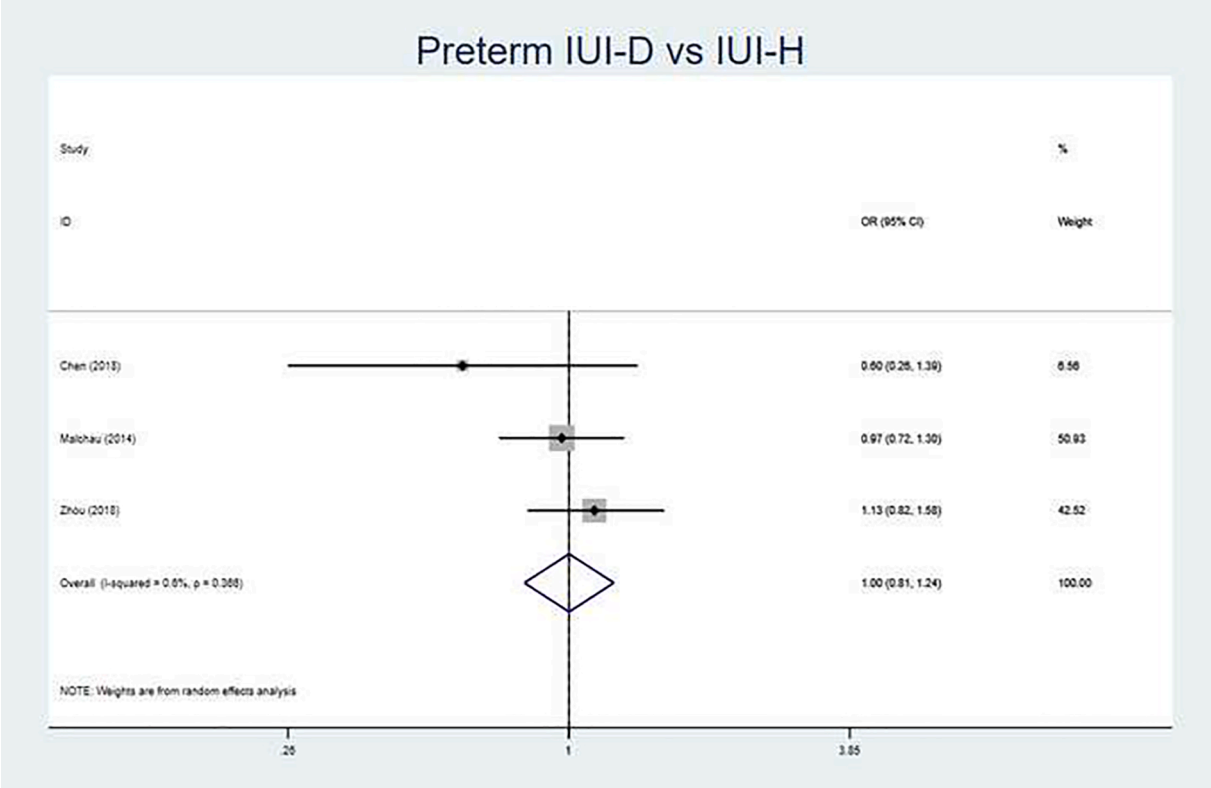

Fig. 5a. Meta-analysis PTB, IUI-D vs IUI-H

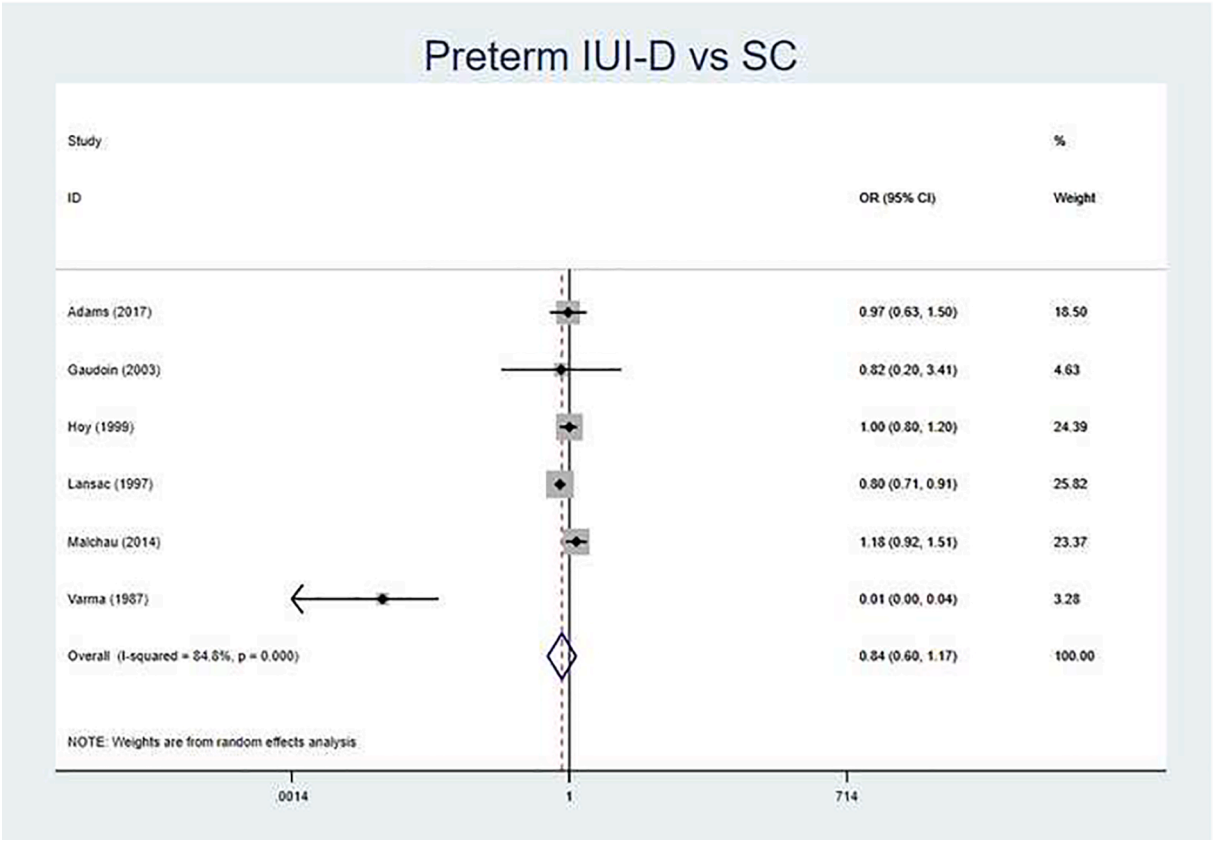

Fig. 5b. Meta-analysis PTB, IUI-D vs SC

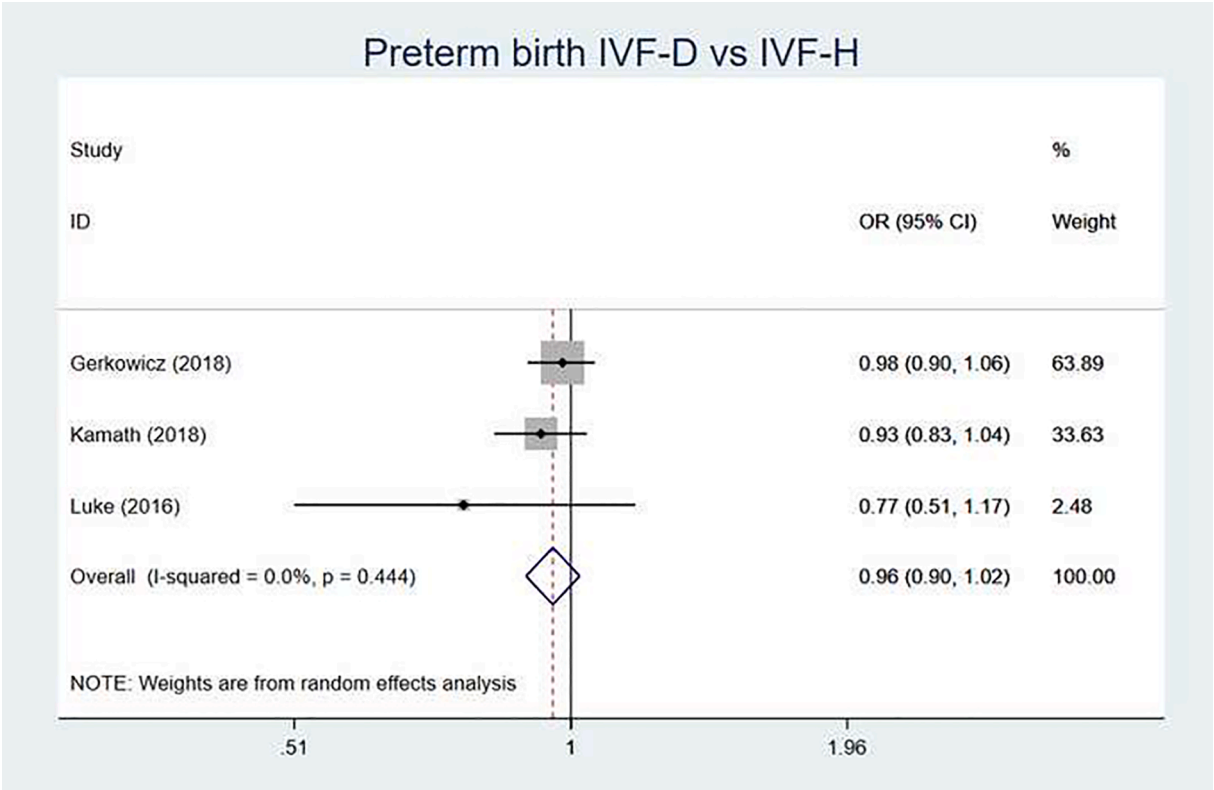

Fig. 5c. Meta-analysis PTB, IVF-D vs IVF-H.

0.84, 95%CI 0.60–1.17) (Fig. 5b). Four studies provided data for singletons only [29–32] and two studies included also multiple pregnancies [12,33]. The risk of bias low in two studies, moderate in two and serious in two studies. IUI-D cohort sizes varied from 35 to 8943. Meta-analysis of only singletons showed no increased risk for PTB in IUI-D vs. SC pregnancies (pooled aOR 0.95, 95%CI 0.73–1.22) (Supplementary Fig. S9).

IVF/ICSI-D vs IVF/ICSI-H

Three studies were included in the meta-analysis for PTB. No increased risk for PTB was found in pregnancies after IVF-D compared to IVF/ICSI-H (pooled OR 0.96, 95%CI 0.90–1.02) (Fig. 5c). The risk of bias was low in one study and moderate in two studies. Cohort sizes varied from 200 to over 6000 births. All studies adjusted for singletons.

Yu et al. (2018) compared singleton pregnancies resulting from the first IVF/ICSI cycle, based on the large SART-CORS register study. Numerous adjustments were made. No difference was found for PTB nor for very PTB between IVF/ICSI-pregnancies using donor sperm or partner sperm [36].

Kamath and colleagues reported that post-term birth was seen more often after IVF/ICSI-D (aOR 1.10, 95%CI 1.03–1.17) [35].

Conclusion: There may be little or no difference in risk of PTB between children born after IUI-D compared both with IUI-H and SC, low certainty of evidence (GRADE ⊕⊕OO) or between children born after IVF/ICSI-D compared with IVF/ICSI-H, respectively, moderate certainty of evidence (GRADE ⊕ ⊕ ⊕ O).

The effect of donor sperm on birth defects

Birth defects were reported in eight original studies (Table 1, 3). Four of them were assessed having either low or moderate risk of bias [12,38–40], and the rest had serious risk of bias. Size of study population ranged from 173 to over 20 000. In general, the rate of births defects after use of donor sperm varied between 0.4 and 8.4 %. The large variance is probably due to varying definitions on birth defects and differences in reporting them e.g. major birth defects vs any birth defects. Similar rates of birth defects were reported in studies comparing IUI-D vs. IUI-H [28,41] and IUI-D vs. SC pregnancies [12,32,39]. Only one study reported an increased risk, but this study was evaluated as having a serious risk of bias [34]. Studies comparing IVF-D and IVF-H showed similar rates of birth defects [32,40].

The effect of donor sperm on offspring sex ratio

Several IUI-D studies reported data on sex ratio among children (Table 1). Studies with comparison groups report no difference in sex ratio after IUI-D treatment compared with IUI-H or SC pregnancies [12,28,30,34].

Discussion

In this systematic review and meta-analysis, a moderately increased risk was observed for PE and HDP after IUI-D compared both with IUI-H and SC pregnancies. However, no increased risk of either HDP or PE was seen when using IVF-D. The frequency of children with LBW or PTB was similar between IUI-D and IUI-H as well as between IUI-D and SC, respectively. The risk for LBW was, however, lower for children born after IVF-D compared with IVF-H.

We conducted separate meta-analyses for singletons (studies that included only singletons or adjusted their results for singletons) to exclude the bias caused by multiple pregnancies. We also conducted a meta-analysis pooling singleton and multiple pregnancies because it showed the full consequence of an IUI program. In a real-life clinical setting, multiple pregnancies cannot be completely avoided in IUI-treatments, even though many clinics have a strict cancellation policy in cases of multi-follicular response prior to IUI-D or IUI-H. Including multiple pregnancies may still introduce a bias, since in many countries natural cycle is more often used in IUI-D treatments and the multiple pregnancy rate is low.

HDP and PE

We found an increased risk of PE and HDP, when comparing IUI-D both with IUI-H and SC pregnancies. An increased risk remained after limiting the meta-analysis to singletons. This indicates that the risk increase is associated with the use of donor sperm, not the IUI treatment itself or the higher rate of multiple pregnancies associated with ovarian stimulation. We found no increased risk of PE or HDP in IVF-D compared with IVF-H pregnancies. Our results are in accordance with earlier meta-analyses showing that compared to use of partner sperm there is an increased risk of PE after IUI-D but, interestingly, not using IVF-D treatment [11,19]. Sensitivity analyses on IVF/ICSI treatments only are important, as these treatments per se have increased risk of HDP. According to the most recent meta-analyses and cohort studies the risk of PE was 1.3 to 1.8 -fold higher in IVF/ICSI than in non-ART singleton pregnancies [42,43]. Most studies included in our meta-analysis adjusted for maternal age. This is important as women receiving IUI-D treatment are often older than their IUI-H treated counterparts, and advanced age is a risk factor for underlying hypertension.

The reason for increased incidence of HDP in IUI-D pregnancies is not clear but impaired immunoregulation due to lack of pre-conceptional exposure to seminal fluid may result in poor placentation and predispose to PE [44]. Several findings support the immunological hypothesis. Preeclampsia is more common in first time pregnancies [45].This effect of less exposure to antigens and higher risk of PE may also explain why Kyrou et al. (2010) found that the fewer the number of IUI-D cycles per woman, the higher the risk of PE [46]. This is supported by other studies showing that the risk of HDP and PE is increased in pregnancies that occur after short duration of exposure to partner sperm [47], or in case of a new partner [48], or after a long interval between pregnancies [49,50].

Perinatal outcomes

In our meta-analyses, no increased risk for LBW or PTB was found in children born after IUI-D compared to IUI-H as well in children born after IUI-D compared to SC. Separate analyses on singletons showed similar results. Singleton analysis is essential, since multiple pregnancy is a risk factor for both LBW and PTB, and IUI treatments might often result in multiple pregnancy and there may be a skewed distribution in multiple pregnancies between IUI-D and IUI-H. Adams et al. (2017) found an increased risk for LBW after IUI-D, but they included studies that did not adjust for multiple pregnancies [29]. Our result of no increased risk of LBW after IUI-D compared to IUI-H is in accordance with the meta-analysis published by Allen et al. (2021) [11].

Most of the included studies comparing IUI-D with IUI-H or SC pregnancies had comparable perinatal outcomes. Some controversial results between studies concerning perinatal outcomes might, at least partly, be due to differences in ovarian stimulation strategies across studies, as ovarian stimulation is known to be associated with adverse perinatal outcomes [31]. In the IUI-H studies use of ovarian stimulation was as high as 70 to 92% [28,31]. On the other hand, natural cycle is generally more often used in IUI-D as the women have often good reproductive health. It is worth mentioning that the practice varied a lot as for example in one small study all women had received ovarian stimulation prior to IUI-D [30].

Generally, IVF pregnancies are known to be associated with higher risk of PTB and LBW compared to SC pregnancies [51]. An interesting finding in our study was that children born after IVF-D had a lower risk for LBW than children born after IVF-H which is in accordance with results recently published by Allen et al. (2021) [11]. The reason for the lower risk of LBW observed in IVF-D vs. IVF-H may be related to the

difference in the patient populations as women receiving IVF-H may have more severe infertility diagnoses, such as tubal pathology, endometriosis, uterine pathology, endocrine disorders compared with those treated with IVF-D. ICSI-H might be a more appropriate control group than IVF-H, as the main indication for ICSI-H is not female factor infertility but severe male factor infertility. On the other hand, the sperm used in IVF-D treatment is usually from healthy donors with top quality semen which is not the case in ICSI-H group. Studies on the influence of low sperm quality on the risk of LBW have reported conflicting results [52,53].

Interpretation of the results

According to our meta-analysis the perinatal outcomes after use of donor sperm are reassuring. In interpretation of the results of the perinatal outcomes, it is important to remember that randomized studies are not possible in this setting, and that the indication for treatment may vary widely both among the study population needing donor sperm and controls. If the IUI-D group comprises single women or same sex female couples often with normal fertility, women with SC pregnancies might be an appropriate control group for comparing obstetric and perinatal outcomes while women receiving IUI-H are less optimal controls as they may have various infertility problems and hence have a greater risk for adverse outcomes [54]. However, we found similar results comparing IUI-D with IUI-H and SC.

Strengths and limitations

The strength of our meta-analyses is that we separated IUI-D and IVF-D and further that we either stratified on plurality or included only studies with adjustment for plurality. The splitting of the control groups in IUI-H, IVF-H and SC pregnancies also added new information on the risk of obstetric and perinatal outcomes compared to the previous reviews.

A limitation of this review is the heterogeneity of the included studies. The splitting of the control groups in IUI-H, IVF-H and SC pregnancies limited the number of studies included in each meta-analysis, decreasing the precision, but made the results more homogenous. Furthermore, most of the studies had a very poor description of the included patient populations, as most studies did not specify the indication for using donor sperm and the proportion of couples with male factor infertility (in combination with or without female infertility) as well as the proportion of single women or women with a female partner is not known. Another limitation is that some studies did not report the type of treatment cycle or a use of ovarian stimulation. Because of differences in patient infertility characteristics and treatment policies between study and control groups bias is likely to occur. Most studies adjusted for maternal age.

Conclusions

Our systematic review and meta-analyses showed that there is a moderately increased risk of PE and HDP in IUI-D pregnancies while the risk of LBW and PTB in children born after IUI-D are comparable to IUI-H and SC. Risks for HDP and PTB after IVF-D are comparable to IVF-H, and there is a slightly lower risk for LBW after IVF-D. From a clinical point of view, the increased risk of HDP after IUI-D treatment identifies a new risk group and calls for case-by-case consideration of prophylactic treatment (e.g. low-dose aspirin) and/or intensified surveillance of these women during pregnancy. In addition, this information should be used for patient counselling.

Key message

There is an increased risk for preeclampsia and hypertensive disorders of pregnancy after IUI-D compared both with IUI-H and spontaneous conception, but not when comparing IVF-D with IVF. Using donor sperm in IUI/IVF does not seem to increase risks for perinatal outcomes such as low birth weight and preterm birth compared with corresponding partner sperm treatments.

Author contributions

E.-M.P., V.S.-A., C.B., A.L., Å.M., A.P., N.O., L.B.R and H.L. contributed to the conception and design of the study. E.-M.P., V.S.-A. and H.L. searched databases, screened abstracts and full papers for inclusion. M. P., C.B. and Å.M. were responsible for performing the statistical analyses. E.-M.P., V.S.-A. and H.L. wrote the manuscript. All authors contributed to the manuscript revision, read and approved the submitted version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by grants from Perklén's foundation and Tampere University Hospital support foundation. We thank librarian Katri Larmo (University of Helsinki) for her help with the literature search. We also thank Gedeon Richter for providing travel, accommodation, and working facilities to the Nordic Collaboration Group.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2022.05.031.

References

[1] Amy M, Quagliarello J. Semen quality before and after processing by a swim-up method: relationship to outcome of intrauterine insemination. Fertil Steril 1987;48(4):643–8.
[2] Bodri D, Nair S, Gill A, Lamanna G, Rahmati M, Arian-Schad M, et al. Shared motherhood IVF: high delivery rates in a large study of treatments for lesbian couples using partner-donated eggs. Reprod Biomed Online 2018;36(2):130–6.
[3] Soares SR, Cruz M, Vergara V, Requena A, García-Velasco JA. Donor IUI is equally effective for heterosexual couples, single women and lesbians, but autologous IUI does worse. Hum Reprod 2019;34:2184–92.
[4] Linara-Demakakou E, Bodri D, Wang J, Arian-Schad M, Macklon N, Ahuja K. Cumulative live birth rates following insemination with donor spermatozoa in single women, same-sex couples and heterosexual patients. Reprod Biomed Online 2020;41:1007–14.
[5] Salomon M, Sylvest R, Hansson H, Nyboe Andersen A, Schmidt L. Sociodemographic characteristics and attitudes towards motherhood among single women compared with cohabiting women treated with donor semen - a Danish multicenter study. Acta Obstet Gynecol Scand 2015;94:473–81.
[6] OECD Family Database n.d. http://www.oecd.org/els/family/database.htm.
[7] Frick AP. Advanced maternal age and adverse pregnancy outcomes. Best Pract Res Clin Obstet Gynaecol 2021;70:92–100.
[8] Frederiksen LE, Ernst A, Brix N, Braskhøj Lauridsen LL, Roos L, Ramlau-Hansen CH, et al. Risk of Adverse Pregnancy Outcomes at Advanced Maternal Age. Obstet Gynecol 2018;131(3):457–63.
[9] Sheen J-J, Wright JD, Goffman D, Kern-Goldberger AR, Booker W, Siddiq Z, et al. Maternal age and risk for adverse outcomes. Am J Obstet Gynecol 2018;219(4):390.e1–390.e15.
[10] Usta I, Nassar A. Advanced maternal age. Part I: obstetric complications. Am J Perinatol 2008;25(08):521–34.
[11] Allen CP, Marconi N, McLernon DJ, Bhattacharya S, Maheshwari A. Outcomes of pregnancies using donor sperm compared with those using partner sperm: systematic review and meta-analysis. Hum Reprod Update 2021;27:190–211.
[12] Hoy J, Venn A, Halliday J, Kovacs G, Waalwyk K. Perinatal and obstetric outcomes of donor insemination using cryopreserved semen in Victoria. Australia Hum Reprod 1999;14:1760–4.
[13] Need JA, Bell B, Meffin E, Jones WR. Pre-eclampsia in pregnancies from donor inseminations. J Reprod Immunol 1983;5(6):329–38.
[14] Smith GN, Walker M, Tessier JL, Millar KG. Increased incidence of preeclampsia in women conceiving by intrauterine insemination with donor versus partner sperm for treatment of primary infertility. Am J Obstet Gynecol 1997;177(2):455–8.

[15] Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol 2020;135:e237–60.
[16] Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007;335(7627):974.
[17] Goffin SM, Derraik JGB, Groom KM, Cutfield WS. Maternal pre-eclampsia and long-term offspring health: Is there a shadow cast? Pregnancy Hypertens 2018;12:11–5.
[18] Adams DH, Gerace A, Davies MJ, de Lacey S. Self-reported physical health status of donor sperm-conceived adults. J Dev Orig Health Dis 2021;12(4):638–51.
[19] González-Comadran M, Avila JU, Tascón AS, Jiménéz R, Solà I, Brassesco M, et al. The impact of donor insemination on the risk of preeclampsia: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2014;182:160–6.
[20] Adams DH, Clark RA, Davies MJ, de Lacey S. A meta-analysis of sperm donation offspring health outcomes. J Dev Orig Health Dis 2017;8(1):44–55.
[21] Adams DH, Clark RA, Davies MJ, de Lacey S. Update on: a meta-analysis of sperm donation offspring health outcomes - 2018 update. J Dev Orig Health Dis 2018;9:561–2.
[22] Attali E, Yogev Y. The impact of advanced maternal age on pregnancy outcome. Best Pract Res Clin Obstet Gynaecol 2021;70:2–9.
[23] Volgsten H, Schmidt L. Motherhood through medically assisted reproduction - characteristics and motivations of Swedish single mothers by choice. Hum Fertil (Camb) 2021;24:219–25.
[24] Storgaard M, Loft A, Bergh C, Wennerholm UB, Söderström-Anttila V, Romundstad LB, et al. Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis. BJOG 2017;124(4):561–72.
[25] Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
[26] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
[27] Kennedy AL, Stern CJ, Tong S, et al. The incidence of hypertensive disorders of pregnancy following sperm donation in IVF: an Australian state-wide retrospective cohort study. Hum Reprod 2019;34:2541–8.
[28] Chen L, Zhu L, Cai C, Yan G, Sun H. Clinical and neonatal outcomes of intrauterine insemination with frozen donor sperm. Syst Biol Reprod Med 2018;64(4):240–5.
[29] Adams D, Fernandez R, Moore V, Willson K, Rumbold A, Lacey S, et al. Sperm donation perinatal outcomes in an Australian population cohort. J Obstet Gynaecol Res 2017;43(12):1830–9.
[30] Gaudoin M, Dobbie R, Finlayson A, Chalmers J, Cameron IT, Fleming R. Ovulation induction/intrauterine insemination in infertile couples is associated with low-birth-weight infants. Am J Obstet Gynecol 2003;188(3):611–6.
[31] Malchau SS, Loft A, Henningsen A-KA, Nyboe Andersen A, Pinborg A. Perinatal outcomes in 6,338 singletons born after intrauterine insemination in Denmark, 2007 to 2012: the influence of ovarian stimulation. Fertil Steril 2014;102:1110-1116.e2.
[32] Lansac J, Thepot F, Mayaux MJ, Czyglick F, Wack T, Selva J, et al. Pregnancy outcome after artificial insemination or IVF with frozen semen donor: a collaborative study of the French CECOS Federation on 21,597 pregnancies. Eur J Obstet Gynecol Reprod Biol 1997;74(2):223–8.
[33] Varma TR, Patel RH. Outcome of pregnancy following investigation and treatment of infertility. Int J Gynaecol Obstet 1987;25(2):113–20.
[34] Huang D, Song S, Liao A. Short-term safety evaluation of the offspring conceived by 7272 artificial insemination cycles with donor spermatozoon. Andrologia 2016;48(7):817–23.
[35] Kamath MS, Antonisamy B, Selliah HY, La Marca A, Sunkara SK. Perinatal outcomes following IVF with use of donor versus partner sperm. Reprod Biomed Online 2018;36(6):705–10.
[36] Yu Bo, Fritz R, Xie X, Negassa A, Jindal S, Vega M, et al. The impact of using donor sperm in assisted reproductive technology cycles on perinatal outcomes. Fertil Steril 2018;110(7):1285–9.
[37] Castillo CM, Horne G, Fitzgerald CT, Johnstone ED, Brison DR, Roberts SA. The impact of IVF on birthweight from 1991 to 2015: a cross-sectional study. Hum Reprod 2019;34:920–31.
[38] Zhou Z, Chen L, Wu H, Zheng D, Li R, Mol BW, et al. Assisted reproductive technology in Beijing, 2013–2015. Reprod Biomed Online 2018;37(5):521–32.
[39] Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, et al. Reproductive technologies and the risk of birth defects. N Engl J Med 2012;366(19):1803–13.
[40] Luke B, Stern JE, Kotelchuck M, Declercq ER, Anderka M, Diop H. Birth outcomes by infertility treatment: analyses of the population-based cohort Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART). J Reprod Med 2016;61:114–27.
[41] Yan J, Huang G, Sun Y, Zhao X, Chen S, Zou S, et al. Birth defects after assisted reproductive technologies in China: analysis of 15,405 offspring in seven centers (2004 to 2008). Fertil Steril 2011;95(1):458–60.
[42] Qin J, Liu X, Sheng X, Wang H, Gao S. Assisted reproductive technology and the risk of pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies: a meta-analysis of cohort studies. Fertil Steril 2016;105:73–6.
[43] Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ 2016;353:i1753.
[44] Redman CWG, Sargent IL. Immunology of pre-eclampsia. Am J Reprod Immunol 2010;63:534–43.
[45] Robillard PY, Hulsey TC, Périanin J, Janky E, Miri EH, Papiernik E. Association of pregnancy-induced hypertension with duration of sexual cohabitation before conception. Lancet 1994;344:973–5.
[46] Kyrou D, Kolibianakis EM, Devroey P, Fatemi HM. Is the use of donor sperm associated with a higher incidence of preeclampsia in women who achieve pregnancy after intrauterine insemination? Fertil Steril 2010;93(4):1124–7.
[47] Einarsson JI, Sangi-Haghpeykar H, Gardner MO. Sperm exposure and development of preeclampsia. Am J Obstet Gynecol 2003;188(5):1241–3.
[48] Robillard P-Y, Hulsey TC, Alexander GR, Keenan A, de Caunes F, Papiernik E. Paternity patterns and risk of preeclampsia in the last pregnancy in multiparae. J Reprod Immunol 1993;24(1):1–12.
[49] Gebremedhin AT, Regan AK, Ball S, et al. Interpregnancy interval and hypertensive disorders of pregnancy: A population-based cohort study. Paediatr Perinat Epidemiol 2021;35:404–14.
[50] van Oostwaard MF, Langenveld J, Schuit E, et al. Prediction of recurrence of hypertensive disorders of pregnancy in the term period, a retrospective cohort study. Pregnancy Hypertens 2014;4:194–202.
[51] Berntsen S, Soderstrom-Anttila V, Wennerholm U-B, et al. The health of children conceived by ART: “the chicken or the egg?”. Hum Reprod Update 2019;25:137–58.
[52] Anderson RE, Hanson HA, Thai D, Zhang C, Presson AP, Aston KI, et al. Do paternal semen parameters influence the birth weight or BMI of the offspring? A study from the Utah Population Database. J Assist Reprod Genet 2018;35(5):793–9.
[53] Kasman AM, Li S, Zhao Q, Behr B, Eisenberg ML. Relationship between male age, semen parameters and assisted reproductive technology outcomes. Andrology 2021;9:245–52.
[54] Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Soderstrom-Anttila V, et al. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. Hum Reprod Update 2013;19(2):87–104.

MD Eeva-Maria Pohjonen is a specialist in obstetrics and gynaecology. She is currently working at the Infertility Clinic at Tampere University Hospital. Her research interests include obstetric and perinatal complications after infertility treatments.