

Assisted Reproductive Technology and Hypertensive Disorders of Pregnancy: Systematic Review and Meta-Analyses

Hui Ju Chih

Queen's University

Flavia Elias

Queen's University

Laura Gaudet

Queen's University

Maria Velez (✉ maria.velez@queensu.ca)

Queen's University

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Abstract

Background

Hypertensive disorders of pregnancy (HDP) is one of the most common pregnancy complications and causes of maternal morbidity and mortality. Many cohort studies were conducted to study adverse pregnancy outcomes associated with pregnancies from assisted reproductive technology. We aimed to comprehensively review all available evidence to date to compare the odds of HDP and preeclampsia between pregnancies achieved by in vitro fertilization (IVF) and spontaneous pregnancies.

Methods

We conducted a systematic review and meta-analysis based on cohort studies identified from EMBASE, MEDLINE, and Cochrane Library (up to 2020) and manually using a structured search strategy. Cohort studies that compared pregnancies after IVF with or without intracytoplasmic sperm fertilization (ICSI) and SC with HDP or preeclampsia as the outcome of interest were included. The control group was women who conceived spontaneously without ART or fertility medications. Studies published in English, French, Chinese, and Portuguese were reviewed. Eligibility and quality of studies were evaluated by two reviewers independently. Quality assessment was conducted using the Newcastle Ottawa Scale (NOS) for Cohort Studies. The pooled results were reported in odds ratios (OR) with 95% confidence intervals based on random effects models. I-squared (I^2) test was used to evaluate heterogeneity and publication bias was assessed using funnel plots.

Results

Seventy-eight studies were included after a screening of 1,879 abstracts and 275 full text articles. Compared to SC, IVF/ICSI singleton pregnancies (OR 1.63; 95% CI 1.54-1.74; $I^2 = 79%$) and multiple pregnancies (OR 1.31; 95% CI 1.18-1.47; $I^2 = 73%$) were both associated with higher odds of HDP. Singleton pregnancies with oocyte donation had the highest odds of HDP out of all groups analyzed (OR 4.11; 95% CI 2.75-6.16; $I^2 = 85%$). Frozen embryo transfer resulted in higher odds of HDP (OR 1.74; 95% CI 1.58-1.92; $I^2 = 55%$) than fresh embryo transfer (OR 1.43; 95% CI 1.33-1.53; $I^2 = 72%$). Similar findings for preeclampsia were also reported.

Conclusions

Our meta-analysis confirmed that IVF/ICSI pregnancies are at high odds of HDP and preeclampsia than SC, irrespective of the plurality. The odds were especially high in frozen embryo transfer and oocyte donation pregnancies.

Background

In 2010, 48.5 million couples worldwide were estimated to be affected by infertility (1). The use of in vitro fertilization (IVF) and other assisted reproductive technologies (ART) is expanding rapidly, accounting for more than seven million births worldwide (2). The advancement of treatments and changes in protocols have also reshaped the landscape of fertility practice in recent years. For example, intracytoplasmic sperm injection (ICSI) is mainly indicated for male factor infertility or poor response to IVF (3); cryopreservation has led to the rise of frozen embryo transfer (FET), which expands the scope of treatment and decreases the risk of ovarian hyperstimulation syndrome (4); finally, oocyte donation (OD) allows women with decreased ovarian reserve or ovarian failure to achieve pregnancy (5).

While ART continues to benefit many couples around the world, it may be associated with adverse outcomes, including hypertensive disorders of pregnancy (HDP) (6–10). HDP, including gestational hypertension and preeclampsia, occur in approximately 12–22% of all pregnancies and is associated with significant maternal and prenatal morbidity and mortality (11). Preeclampsia is associated with a wide range of complications related to microangiopathy, vasoconstriction, and malperfusion. Women with a history of preeclampsia also continue to be at a high risk for cardiovascular disease, chronic

kidney disease, and cardiovascular mortality even after pregnancy (12). The pregnancy and postpartum complications as well as high mortality rates highlight the importance of prevention and early detection of HDP.

Different ART seem to carry different risks of maternal and perinatal outcomes (13). Our systematic review and meta-analysis aim to understand whether IVF/ICSI pregnancies are associated with increased odds of HDP and preeclampsia in comparison to spontaneous conception (SC); furthermore, we aim to understand whether the odds differ depending on types of procedure. Together, this review may inform clinical recommendations for women planning to achieve pregnancy through IVF/ICSI.

Methods

Search strategy

The study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (Supplementary information, Additional file 1) and the protocol was registered and available on Open Science Framework (DOI: <https://osf.io/562jr/>). A search strategy was developed under the support of a research librarian to identify studies evaluating the incidence of HDP and/or preeclampsia in IVF or ICSI pregnancies compared to SC (Additional file 2). MeSH terms and selection criteria were based on the Patient, Intervention, Comparison and Outcome statement. Cohort studies published from the earliest available publication to April 2020 were retrieved from Medline, Embase, and Cochrane Central Register of controlled Trials using the OVID platform. A manual search of previously published systematic reviews and meta-analysis was also conducted to identify other eligible studies.

Selection of studies

Both abstract and full text screening were performed by two reviewers (HC, FTSE). In the first screening, articles were selected based on titles and abstracts. The second screening involved full-text reviews, where studies were evaluated based on a set of eligibility criteria. Any conflict was resolved by consensus or the involvement of a third team member (MPV).

Cohort studies that compared pregnancies after IVF or ICSI and SC with HDP or preeclampsia as the outcome of interest were included. The control group consisted of women who conceived spontaneously without the use of ART or fertility medications. The exposure group consisted of singleton or multiple IVF pregnancies. Studies were excluded if they were not cohort studies, not in English, French, Portuguese, or Chinese, included patients undergoing ART or fertility treatments other than IVF/ICSI, did not specify the type of ART used, or did not clearly separate patients into singleton or multiple pregnancies. Case-control studies were not included due to known risks of selection and recall biases. Studies that included a subgroup of women (e.g. advanced maternal age, obesity) were not included in the general singleton and multiple gestation analyses as they were not representative of the general population. However, they were included in sub-analyses for type of embryo transfer (fresh embryo transfer (fresh ET) or FET) and OD. For studies with overlapping cohorts, where the same database was used for analyses, only the most recent study was included in the meta-analysis. A complete list of excluded studies after full text screening with their respective reasons of exclusion may be found in Additional file 3.

Outcomes of interest included HDP and preeclampsia. Hypertensive disorders of pregnancy describe any hypertensive effects that is observed during pregnancy, including pre-existing hypertension, gestational hypertension and preeclampsia.

Preeclampsia was defined as hypertension that develops for the first time after 20 weeks of gestation with one or more of the following: proteinuria, adverse conditions, or severe complications (14).

Data extraction and quality assessment

Data was extracted manually and entered into an Excel spreadsheet by a reviewer (HC). The following characteristics of each study were collected: authorship, year of publication, country, study design, search database, time period of the cohort, matching factors, statistical analysis, outcome of interest, definition of outcome, mean maternal age, mean BMI, number of patients with chronic hypertension, type of ART, type of infertility, source of oocyte, method of embryo transfer, sample size, and crude data. If needed, percentages of HDP and preeclampsia were converted to crude data based on the sample size.

Study quality was assessed using the Newcastle-Ottawa Scale for Cohort Studies (15). Each study was scored out of nine based on eight items across three domains: the selection of study groups (4 items), comparability of groups (1 item), and ascertainment of exposure or outcome of interest in cohort studies, respectively (3 items). It was then determined to have either high quality (8 or 9), moderate quality (6 or 7), or low quality (less than 5) based on the total NOS score. A second reviewer (FTSE) reviewed all data extraction and quality assessment performed.

Statistical analysis

The meta-analyses were performed using Review Manager (RevMan) version 5.4. Cohort studies were included in the general meta-analyses by plurality. In addition, separate analyses on fresh ET, FET, and OD were also conducted. Results were reported as odds ratios with corresponding 95% confidence intervals based on random effects models, which assumed heterogeneity of the data. The Mantel-Haenszel method was used to calculate overall odds ratios. Statistical significance was determined by a P value of equal or less than 0.05. Sensitivity analysis was carried out by removing one study at a time to assess the effect of the study on the results. If the measure of association without the chosen study fell outside of the confidence interval, the study was said to have a significant influence (16). I-squared (I^2) test was used to evaluate heterogeneity, with an I^2 value of greater than 50% being considered as high heterogeneity (17). Risk of publication bias was evaluated using funnel plots if the meta-analysis included 10 or more studies (18).

Results

Study selection

Our search strategy identified 2674 studies and 1879 citations were eligible for abstract and title screening after removing duplicates. Finally, 78 studies met the inclusion criteria and were included in the meta-analysis (Fig. 1). Six studies had overlapping cohorts with more recently published studies and thus were excluded (Additional file 3).

Characteristics of included studies

The characteristics of all included studies, which involved 355,382 IVF/ICSI pregnancies and 7,503,182 SC, may be found in Table 1. The sizes of the exposure (IVF/ICSI) and control (SC) groups ranged from 19 to 83,582 pregnancies and from 21 to 1,382,311 pregnancies respectively. Out of the 78 studies included, 19 were population-based cohort studies conducted in Canada (19–21), Denmark (22), Finland (23, 24), Israel (25), Italy (26), Japan (27), Netherlands (28), Norway (29), Slovenia (30), Sweden (31–34), and the United States (35, 36). Two studies were conducted across multiple European countries (37, 38). Forty-seven studies looked at the incidences of preeclampsia or HDP in IVF/ICSI singleton pregnancies in comparison to SC, while 38 studies investigated the outcomes of multiple pregnancies in particular (Table 1). Based on their respective NOS scores, 14 studies had a high methodological quality, 55 studies had a moderate quality, and nine had a low quality (Table 1, Additional file 4). Thirty studies were matched cohort studies using varying factors such as maternal age, birth year, parity, socioeconomic status, location (Table 1). Six studies used chronic hypertension to adjust the comparability between exposure and control groups (21, 37, 39–42). One study calculated propensity scores that account for 27 maternal and paternal variables (41).

Table 1
 Characteristics of 78 included cohort studies. S = Singleton pregnancy, M = Multiple pregnancy.

First author, Publication year, Country	Type of cohort	Years of the cohort	Matching factors	Comparison groups	Pregnancies conceived by IVF/ICSI (n)	Spontaneous pregnancies (n)	NOS Score
Agarwal, 2005, Singapore (66)	Hospital-based Retrospective	1998–1999	Maternal age, sex, date of delivery, race, plurality and parity	IVF/ICSI, ICSI alone	(S) 41 (M) 35	(S) 147 (M) 114	7
Ai, 2005, China (67)	Hospital-based Retrospective	1998–2004	No	IVF/ICSI	(M) 47	(M) 98	6
Apantaku, 2008, UK (68)	Hospital-based Retrospective	1999–2004	Maternal age, parity	IVF/ICSI	(S) 88	(S) 88	8
Aydin, 2016, Turkey (69)	Hospital-based Retrospective	2007–2010	Maternal age	IVF/ICSI	(M) 137	(M) 133	8
Barda, 2017, Israel (70)	Hospital-based Retrospective	2009–2015	No	IVF/ICSI	(M) 449	(M) 259	6
Barua, 2016, Australia (71)	Hospital-based Retrospective	2007–2010	No	IVF/ICSI, ICSI alone	(S) 470	(S) 48654	6
Beltran Anzola, 2019, France (72)	Hospital-based Retrospective	1995–2015	Maternal age, exact year of birth, parity, sex	IVF/ICSI, Fresh embryo transfer, Frozen embryo transfer	(S) 2327	(S) 6981	7
Bensdorp, 2016, Netherlands (28) (a)	Population-based Retrospective	2000–2012	Zygosity, parity, socioeconomic status, conception method	IVF/ICSI, ICSI alone	(M) 2437	(M) 3276	7
Beyer, 2016, Germany (73)	Hospital-based Retrospective	N/A (13-year period)	No	IVF/ICSI, Fresh embryo transfer, Frozen embryo transfer	(S) 467	(S) 6417	6
Carbone, 2011, UK (74)	Hospital-based Prospective	2006–2009	No	IVF/ICSI	(S) 426	(S) 26538	7
Caserta, 2008, Italy (26)	Hospital-based Prospective	2004–2006	Parity, age, height, weight, ethnic origin, smoking, history of infertility	IVF/ICSI, ICSI alone	(S) 364	(S) 304	3
Caserta, 2014, Italy (75)	Hospital-based Retrospective	2007–2011	No	IVF/ICSI	(M) 138	(M) 207	7

First author, Publication year, Country	Type of cohort	Years of the cohort	Matching factors	Comparison groups	Pregnancies conceived by IVF/ICSI (n)	Spontaneous pregnancies (n)	NOS Score
Choi, 2006, Korea (76)	Hospital-based Retrospective	1994–2003	No	IVF/ICSI	(M) 190	(M) 347	6
Daniel, 2000, Israel (77)	Hospital-based Retrospective	1996–1997	No	IVF/ICSI	(M) 104	(M) 121	7
Dayan, 2015, Canada (78)	Hospital-based Retrospective	2001–2008	No	IVF/ICSI	(S) 326	(S) 9175	7
Dayan, 2016, Canada (20)	Population-based Retrospective	2006–2012	No	IVF/ICSI	(S) 5371	(S) 795997	7
Dayan, 2018, Canada (19)	Population-based Retrospective	2013–2014	No	IVF/ICSI	(S) 1596	(S) 112813	6
Deltombe-Bodart, 2017, France (79)	Hospital-based Retrospective	1997–2014	No	IVF/ICSI, ICSI alone	(M) 360	(M) 986	6
Dior, 2018, Israel (58)	Hospital-based Retrospective	1995–2012	No	Oocyte Donation	(S) 135	(S) 270	7
Elenis, 2015, Sweden (31)	Population-based Retrospective	2005–2008	Age	IVF/ICSI, Oocyte Donation	(S) 139	(M) 150	7
Ernstad, 2019, Sweden (32)	Population-based Retrospective	2005–2015	No	IVF/ICSI, Fresh embryo transfer	(S) 34091	(S) 1127566	6
Fan, 2013, China (80)	Hospital-based Retrospective	2010–2013	No	IVF/ICSI, ICSI alone	(M) 162	(M) 213	7
Farhi, 2013, Israel (81)	Hospital-based Prospective	2006–2008	No	IVF/ICSI, ICSI alone	(S) 509	(S) 587	5
Geipel, 2001, Germany (82)	Hospital-based Retrospective	1995–1999	Maternal age, parity, plurality	IVF/ICSI, ICSI alone	(S) 114 (M) 32	(S) 114 (M) 32	8
Gocmen, 2015, Turkey (83)	Hospital-based Retrospective	2011–2014	No	IVF/ICSI	(M) 19	(M) 65	8
Gojnic, 2005, Serbia (84)	N/A	N/A	Age, education, parity	IVF/ICSI	(M) 120	(M) 120	2
Howe, 1990, US (85)	Hospital-based Retrospective	N/A (first 100 clinical pregnancies conceived in the IVF program)	Age, race, parity, pre-existing medical problem, DES exposure, insurance status	IVF/ICSI	(S) 54	(S) 54	7

First author, Publication year, Country	Type of cohort	Years of the cohort	Matching factors	Comparison groups	Pregnancies conceived by IVF/ICSI (n)	Spontaneous pregnancies (n)	NOS Score
Jancar, 2018, Slovenia (30)	Population-based Retrospective	2002–2015	No	IVF/ICSI	(S) 5837	(S) 261881	7
Jeve, 2016, UK (59)	Hospital-based Retrospective	2007–2014	Age	IVF/ICSI, Oocyte donation	(S) 90	(S) 45	8
Katalinic, 2004, Germany (86)	Hospital-based Prospective	1998–2000; 1993–2001 (control)	No	IVF/ICSI, ICSI alone, Fresh embryo transfer	(S) 2055 (M) 632	(S) 7861 (M) 77	6
Koivurova, 2002, Finland (23)	Population-based Retrospective	1990–1995	Sex of the child, birth year, area of residence, parity, maternal age, social class (defined by occupation)	IVF/ICSI, Fresh embryo transfer	(S) 153 (M) 62	(S) 580 (M) 82	7
Korosec, 2016, Slovenia (87)	Hospital-based Retrospective	2004–2011	Age, parity, hospital	IVF/ICSI, Fresh embryo transfer, Frozen embryo transfer	(S) 1127	(S) 3381	7
Kouhkan, 2018, Iran (88)	Hospital-based Prospective	2014–2017	No	IVF/ICSI	(S) 260	(S) 314	7
Kuivasaari-Pirinen, 2012, Finland (89)	Hospital-based Retrospective	1996–2007	No	IVF/ICSI	(S) 255	(S) 26870	7
Lee, 2015, US (90)	Hospital-based Retrospective	2007–2009	No	IVF/ICSI	(S) 108	(S) 2284	7
Lei, 2019, China (91)	Hospital-based Retrospective	2013–2015	No	IVF/ICSI	(S) 2256 (M) 803	(S) 6667 (M) 101	6
Li, 2015, China (92)	Hospital-based Retrospective	2009–2011	No	IVF/ICSI	(M) 108	(M) 144	6
Luke, 2019, US (35)	Population-based Retrospective	2004–2013 (depending on states)	No	IVF/ICSI, Oocyte donation	(M) 58920	(M) 34033	7

First author, Publication year, Country	Type of cohort	Years of the cohort	Matching factors	Comparison groups	Pregnancies conceived by IVF/ICSI (n)	Spontaneous pregnancies (n)	NOS Score
Luke, 2020, US (36)	Population-based Retrospective	2004–2013 (depending on states)	No	IVF/ICSI, Fresh embryo transfer, Frozen embryo transfer, Oocyte donation	(S) 83582	(S) 1382311	6
Malchau, 2013, Denmark (22)	Population-based Retrospective	1995–2010	Date and year of birth	IVF/ICSI, ICSI alone, Oocyte donation	(S) 15741 (M) 8564	(S) 31010 (M) 25012	7
Meyer, 2020, Israel (60)	Hospital-based Retrospective	2011–2018	Age	Oocyte donation	(S) 159	(S) 73	7
Mohammed, 2012, Qatar (93)	Hospital-based Retrospective	2002–2011	No	IVF/ICSI	(M) 145	(M) 175	7
Moini, 2012, Iran (44)	Hospital-based Prospective	2008–2010	No	IVF/ICSI, ICSI alone	(M) 230	(M) 170	6
Nagata, 2019, Japan (27)	Population-based Retrospective	2011–2014	No	IVF/ICSI, ICSI alone	(S) 2993 (M) 129	(S) 88873 (M) 625	7
Nassar, 2003, Lebanon (39)	Hospital-based Retrospective	1995–2000	Age, parity	IVF/ICSI	(M) 56	(M) 112	9
Nejdet, 2016, Sweden (33)	Population-based Retrospective	2003–2012	No	IVF/ICSI, Fresh embryo transfer, Frozen embryo transfer, Oocyte donation	(S) 27084	(S) 999804	7
Ochsenkuehn, 2003, Germany (94)	Hospital-based Retrospective	1991–1996	Maternal age, gestational age, parity	IVF/ICSI	(S) 163 (M) 65	(S) 322 (M) 78	8
Okby, 2018, Israel (25)	Population-based Retrospective	1988–2010	No	IVF/ICSI	(M) 465	(M) 3053	8
Olivennes, 1993, France (95)	Hospital-based Retrospective	1987–1989	No	IVF/ICSI	(S) 162	(S) 5096	6
Opdahl, 2015, Sweden, Denmark, Norway (37)	Population-based Retrospective	1988–2007	Parity, birth year	IVF/ICSI	(M) 10918	(M) 46674	9

First author, Publication year, Country	Type of cohort	Years of the cohort	Matching factors	Comparison groups	Pregnancies conceived by IVF/ICSI (n)	Spontaneous pregnancies (n)	NOS Score
Poikkeus, 2007, Finland (96)	Hospital-based Retrospective	1997–2003	Year, place of residence	IVF/ICSI, Fresh embryo transfer	(S) 499	(S) 15037	7
Qin, 2017, China (97)	Hospital-based Prospective	2013–2016	No	IVF/ICSI	(S) 1260	(S) 2480	6
Raisanen, 2013, Finland (24)	Population-based Retrospective	2006–2010	No	IVF/ICSI	(S) 5647	(S) 285357	7
Reismullerova, 2015, Slovakia (98)	Hospital-based Retrospective	N/A	No	IVF/ICSI	(S) 526	(S) 15874	7
Reubinoff, 1997, Israel (99)	Hospital-based Retrospective	1983–1993	Maternal ethnic origin, age, parity, location and date of delivery	IVF/ICSI	(S) 260	(S) 260	7
Rizzo, 2016, Italy (40)	Hospital-based Prospective	2007–2014	Maternal age	IVF/ICSI, Fresh embryo transfer, Frozen embryo transfer	(S) 266	(S) 266	9
Sazonova, 2012, Sweden (34)	Population-based Retrospective	2002–2006	No	IVF/ICSI, Fresh embryo transfer, Frozen embryo transfer	(S) 11292	(S) 571914	7
Shi, 2018, China (100)	Hospital-based Retrospective	2013–2016	No	IVF/ICSI	(M) 850	(M) 250	5
Silberstein, 2014, Israel (101)	Hospital-based Retrospective	1988–2006	No	IVF/ICSI	(S) 1294	(S) 171513	6
Stojnic, 2013, Serbia (102)	Hospital-based Retrospective	2006–2010	Maternal age, parity, education, time and place of delivery, BMI	IVF/ICSI, Fresh embryo transfer	(S) 634	(S) 634	7
Sun, 2009, Canada (21)	Population-based Retrospective	2004–2007	Maternal age, parity	IVF/ICSI	(S) 870	(S) 3433	9
Sun, 2016, China (103)	Hospital-based Retrospective	2010–2014	No	IVF/ICSI	(M) 411	(M) 742	7
Suzuki, 2010, Japan (104)	Hospital-based Retrospective	2000–2007	No	IVF/ICSI	(M) 64	(M) 76	6

First author, Publication year, Country	Type of cohort	Years of the cohort	Matching factors	Comparison groups	Pregnancies conceived by IVF/ICSI (n)	Spontaneous pregnancies (n)	NOS Score
Szymusik, 2012, Poland (105)	Hospital-based Retrospective	2005–2009	No	IVF/ICSI, Fresh embryo transfer	(M) 43	(M)83	4
Szymusik, 2018, Poland (106)	Hospital-based Prospective	2013–2016	No	IVF/ICSI	(S) 183	(S) 368	4
Tan, 1992, UK (107)	Hospital-based Retrospective	1978–1987	Maternal age	IVF/ICSI	(S) 494 (M) 125	(S) 978 (M) 21	6
Tandberg, 2015, Norway (29)	Population-based Retrospective	1988–2009	Parity	IVF/ICSI	(S) 12440	(S) 1097084	8
Tomic, 2011, Croatia (108)	Hospital-based Retrospective	2006–2009	Ethnicity, age, gravidity, smoking habits, BMI, weight gain in pregnancy, site and time of delivery	IVF/ICSI, Fresh embryo transfer	(S) 283	(S) 283	7
Vasario, 2012, Italy (109)	Hospital-based Prospective	2004–2008	No	IVF/ICSI	(M) 84	(M) 139	6
Von Versen-Hoynck, 2019, US (50)	Hospital-based Prospective	2011–2017	No	IVF/ICSI, Fresh embryo transfer, Frozen embryo transfer	(S) 367	(S)143	5
Watanabe, 2014, Japan (41)	Hospital-based Retrospective	2009–2011	Closest propensity score (accounting for 27 maternal and paternal variables)	IVF/ICSI	(S) 474	(S) 474	9
Wennberg, 2016, Sweden, Denmark, Finland, Norway (38)	Population-based Retrospective	1982–2007	Parity, year and month of birth	IVF/ICSI, Fresh embryo transfer	(S) 39919	(S) 260166	7
Wu, 2010, China (110)	Hospital-based Retrospective	2006–2008	No	IVF/ICSI	(M) 204	(M) 255	4
Xu, 2005, China (111)	Hospital-based Retrospective	2001–2003	No	IVF/ICSI	(M) 41	(M) 44	4
Yang, 2011, Korea (112)	Hospital-based Retrospective	1995–2008	No	IVF/ICSI	(M) 67	(M) 143	7

First author, Publication year, Country	Type of cohort	Years of the cohort	Matching factors	Comparison groups	Pregnancies conceived by IVF/ICSI (n)	Spontaneous pregnancies (n)	NOS Score
Zadori, 2003, Hungary (113)	Hospital-based Retrospective	1995–2002	Maternal age, parity, gravidity, previous obstetrics outcomes	IVF/ICSI	(S) 185 (M) 36	(S) 185 (M) 36	6
Zhang, 2015, China (114)	Hospital-based Retrospective	2010–2014	No	IVF/ICSI	(M) 53	(M) 128	6
Zhu, 2016, China (42)	Hospital-based Retrospective	2006–2014	Maternal age, birth year	IVF/ICSI	(S) 1659 (M) 982	(S) 5193 (M) 89	9

Specific outcomes

IVF/ICSI Singleton Pregnancies

Forty-seven studies including 265,391 pregnancies in the IVF/ICSI group and 7.4 million pregnancies in the SC group were included in the analysis of HDP. The overall odds ratio (OR) was 1.63 (95% CI 1.54–1.74) with high heterogeneity ($I^2 = 79\%$) (Fig. 2). Almost all studies were of high or moderate quality according to their NOS scores; four were categorized as low quality.

Of those studies above, 26 studies specifically reported the incidence of preeclampsia, resulting in a sample size of 118,637 pregnancies in the IVF/ICSI group and 4.5 million pregnancies in the SC group. Cumulative incidences found that the IVF/ICSI group had significantly higher odds of preeclampsia than the SC group with an OR of 1.59 (95% CI 1.46–1.73) with high heterogeneity ($I^2 = 72\%$) (Additional file 5). Twenty-five studies were classified as high or moderate quality, and one study received an NOS score of low quality. Half of the included studies matched the control group with IVF/ICSI group by maternal factors such as age or parity.

The sub-analysis of eight studies that included ICSI pregnancies only found that this type of procedure had a higher rate of HDP in comparison to SC. The resulting OR was 1.57 (95% CI 1.25–1.98; $I^2 = 72\%$) (Fig. 2). In the case of preeclampsia, only two studies were eligible with no significant difference between the two groups (OR 0.98, 95% CI 0.38–2.51; $I^2 = 72\%$) (Additional file 5). Both pooled analyses showed high heterogeneity.

IVF/ICSI Multiple Pregnancies

Thirty-three studies assessed HDP in twin pregnancies. Higher odds were observed in the IVF/ICSI group than the SC group, with an OR of 1.31 (95% CI 1.18–1.47) with high heterogeneity ($I^2 = 73\%$) (Fig. 3). The number of studies that were rated as high, moderate, and low quality by NOS scores were 8, 25, and 5 respectively.

Sixteen studies assessed preeclampsia as the outcome of interest. The odds of preeclampsia were higher in pregnancies resulting from IVF/ICSI than SC (OR 1.14, 95% CI 1.06–1.23) with no heterogeneity ($I^2 = 0\%$) (Additional file 5). All studies either had moderate or high quality.

For ICSI pregnancies, nine studies were eligible for the analysis of HDP. Overall, no increase in the risk of HDP was observed in the exposure group (OR 1.06, 95% CI 0.85–1.34; $I^2 = 66\%$) (Fig. 3). Five studies reported data on preeclampsia in pregnancies after ICSI. The odds of preeclampsia were slightly higher in pregnancies resulting from ICSI than SC (OR 1.11, 95% CI 1.00–1.24) in the pooled analysis with no heterogeneity ($I^2 = 0\%$) (Additional file 5).

Fresh and Frozen Embryo Transfer

Sixteen studies reported on the relationship between fresh ET and HDP. The pooled result showed that, when compared to SC, fresh ET is associated with increased odds of HDP with an OR of 1.43 (95% CI 1.33–1.53; $I^2 = 72\%$) (Fig. 4). A similar finding was also found in the pooled result of eight studies using preeclampsia as the outcome of interest (OR 1.48, 95% CI 1.37–1.60) with low heterogeneity ($I^2 = 39\%$) (Additional file 5).

FET was also associated with higher odds of HDP and preeclampsia compared to SC. Nine studies were included resulting in a pooled OR of 1.74 (95% CI 1.58–1.92; $I^2 = 55\%$) for HDP (Fig. 4). Comparably, in five studies that studied preeclampsia, the OR was 1.82 (95% CI 1.71–1.95) with no heterogeneity between included studies ($I^2 = 0\%$) (Additional file 5).

Oocyte Donation

Singleton pregnancies resulting from OD were found to have the highest risk of hypertensive complications of all analyses conducted for the study. For HDP, seven studies resulted in a pooled OR of 4.11 (95% CI 2.75–6.16; $I^2 = 85\%$) (Fig. 5). Similar findings were observed in multiple pregnancies, with an OR of 2.62 (95% CI 2.46–2.79) with no heterogeneity ($I^2 = 0\%$). However, only two studies were eligible (Fig. 5).

Five studies studied preeclampsia as the outcome of interest. The resulting OR was 4.96 (95% CI 3.52–7.00) with low heterogeneity ($I^2 = 29\%$) (Additional file 5). All included studies had a moderate or high quality according to their NOS scores.

Overall, with the exception of multiple pregnancy resulting from ICSI, all exposure groups were associated with increased odds of HDP in comparison to SC. Similarly, all study groups except ICSI singleton pregnancies were associated with higher odds of preeclampsia. All findings described above were summarized in Table 2.

Table 2
Summary of results by type of ART and outcome of interest. * = Statistically significant.

Experimental	Number of studies	ART study size (n)	SC study size (n)	OR; 95% CI	I ² (%)	P value
Hypertensive Disorders of Pregnancy						
IVF/ICSI singleton	47	265,391	7,380,862	1.63 (1.54–1.74)	79	< 0.01*
ICSI singleton	8	10,371	177,550	1.57 (1.25–1.98)	72	< 0.01*
IVF/ICSI multiple	38	88,287	118,424	1.31 (1.18–1.47)	73	< 0.01*
ICSI multiple	9	6,581	30,505	1.06 (0.85–1.34)	66	0.60
Fresh embryo transfer singleton	16	162,867	4,381,981	1.43 (1.33–1.53)	72	< 0.01*
Frozen embryo transfer singleton	9	41,462	4,090,152	1.74 (1.58–1.92)	55	< 0.01*
Oocyte donation singleton	7	1,152	78,897	4.11 (2.75–6.16)	85	< 0.01*
Oocyte donation multiple	2	10,488	59,045	2.62 (2.46–2.79)	0	< 0.01*
Preeclampsia						
IVF/ICSI singleton	26	118,637	4,509,780	1.59 (1.46–1.73)	72	< 0.01*
ICSI singleton	2	5,807	31,124	0.98 (0.38–2.51)	72	0.97
IVF/ICSI multiple	16	14,792	34,287	1.14 (1.06–1.23)	0	< 0.01*
ICSI multiple	5	5,618	29,519	1.11 (1.00–1.24)	0	0.05*
Fresh embryo transfer singleton	8	55,300	2,715,647	1.48 (1.37–1.60)	39	< 0.01*
Frozen embryo transfer singleton	5	19,216	2,699,693	1.82 (1.71–1.95)	0	< 0.01*
Oocyte donation singleton	5	973	1,030,587	4.96 (3.52–7.00)	29	< 0.01*

Sensitivity analysis and publication bias

Sensitivity analyses were performed to identify individual studies with large influences on the overall risk estimates. Exclusion of any study did not yield significantly different OR, with the exception of one study by Malchau et al. for the analysis of preeclampsia in IVF/ICSI multiple pregnancies (Additional file 6). Funnel plots of meta-analyses involving more than 10 studies did not reveal any publication bias (Additional file 5).

Discussion

Principle findings

IVF/ICSI pregnancies, when compared to SC, carried higher odds of HDP and preeclampsia regardless of their plurality. While both fresh ET and FET were found to have odds of hypertensive complications, FET was associated with higher odds in comparison fresh ET. Pregnancies resulting from OD had the highest odds of HDP and preeclampsia out of all the groups analyzed.

Analyses on ICSI pregnancies specifically yielded mixed results. In singleton pregnancy, while ICSI resulted in higher odds of HDP compared to SC, the odds of preeclampsia were similar in both groups. In multiple pregnancy, although ICSI was associated with increased odds of preeclampsia, the difference with SC was small.

Comparison with existing literature

Our results of higher odds of HDP and preeclampsia in singleton pregnancy following IVF/ICSI were in accordance with other previous meta-analyses (6, 7, 10, 43). Multiple pregnancy following IVF/ICSI was also found to be at higher odds for preeclampsia and HDP, although the differences were smaller. This was likely because HDP and preeclampsia are known have a higher prevalence in multiple pregnancies than singleton pregnancies, resulting in higher risks of hypertensive complications in both SC and IVF/ICSI groups (44). The meta-analysis by Qin et al. published in 2015 comprehensively studied the risk of HDP in IVF/ICSI multiple pregnancy. However, the study was limited by including other fertility treatments, such as ovulation induction and intrauterine insemination, in the control group, potentially underestimating the risk of IVF/ICSI on the outcome of interest. This might explain the slightly lower relative risk (RR 1.13; 95% CI 1.02–1.26) in comparison to our findings (OR 1.31; 95% CI 1.18–1.47) (9).

Although the mechanism by which IVF/ICSI increases the risk of preeclampsia remains unknown, the presence of significant differences in the outcomes between fresh ET, FET, and OD pregnancies highlighted the potential role of the procedure on the development of hypertensive complications. However, given that a significant amount of cohort studies did not use matching for controls, maternal factors, such as age, parity, and medical comorbidities (including chronic hypertension and diabetes mellitus), as well as unaccounted confounders could still contribute to the observed differences (29). The underlying infertility diagnosis may also lead to varying maternal and perinatal outcomes, as suggestive by Stern and colleagues. The large-scale cohort study found that women with infertility due to tubal factors and ovulation disorders may be at a particularly high risk of HDP in comparison to their respective control groups with the same diagnoses (8). However, there is currently a limited amount of literature on this topic and more thorough analyses may be needed.

When studying ICSI pregnancies separately, our study found varying results for preeclampsia and HDP, and the findings were consistent with those reported by Thomopoulos and colleagues. While the meta-analysis by Thomopoulos et al. was limited by the small number of available studies, our sub-analysis included more recent studies and yielded similar findings (10). Further research on ICSI pregnancies, as well as their indications for the procedure, such as male infertility, should be conducted to identify potential contributing factors.

In recent years, the use of cryopreservation has expanded widely from women with medical indications (e.g. with medical conditions or treatments that impairs fertility) to social embryo and oocyte freezing, including women who prefer to defer childbearing and transgender people as a part of their medical transition process (45). There is a growing interest in the “freeze-all” strategy as a result of its decreased incidence of ovarian hyperstimulation syndrome without compromising live birth rates (45). While FET carries many unique advantages, it is still important to understand the associated perinatal outcomes with the procedure. Our review of all available literature showed that both fresh ET and FET were associated with increased risks of preeclampsia and HDP in comparison to SC; furthermore, the observed differences were greater in FET pregnancies than fresh ET pregnancies, which was consistent with earlier evidence (46–48). It is worth noting that most past literature used fresh ET as a control group instead, making it difficult to directly compare the results between studies.

The observed difference between fresh ET and FET may be explained by the absence of a corpus luteum (CL), as suggested by five recently published cohort studies (32, 49–52). SC typically develop under the presence of one CL, while the number of CL for IVF pregnancies varies depending on the type of procedure. Fresh IVF cycles typically involve more than one CL, whereas

frozen IVF cycles and OD are usually performed under programmed cycles with exogenous hormones in the absence of a CL (49, 52).

von Versen-Hoynck and colleagues performed a prospective cohort study showing that women who conceived without a CL had a higher risk of preeclampsia than women with one or more CL. In the same paper, further analysis also demonstrated that programmed FET pregnancies were associated with higher incidences of preeclampsia than natural FET pregnancies, which had a comparable risk as fresh IVF pregnancies (50). This finding was again supported by Luke and colleagues (52). These studies proposed that performing FET during a natural cycle or with supplementation of missing hormones, such as relaxin, may potentially reduce the risk of preeclampsia and HDP. However, this theory alone could not explain the increased risk in fresh ET in comparison to SC, suggesting that there may be other components of the procedure or unaccounted confounders that increased the risk of hypertensive complications. As fresh ET pregnancies were found to be associated with other perinatal complications such as low birth weight and small for gestational age, it is important to balance the risks and benefits with each patient's health status when considering treatment options (53).

OD is becoming a common standard practice for patients with reproductive disorders, diminished ovarian reserve, or advanced maternal age due to its relatively high success rate and comparable live delivery rates in comparison to autologous IVF pregnancies (54, 55). In our study, women who achieved singleton pregnancies from donated oocytes carried four- to five-fold odds of preeclampsia and HDP in comparison to women who achieved pregnancy through SC. Multiple pregnancies from OD also had higher odds, although the differences with spontaneous multiple pregnancies were smaller.

This finding was consistent with other previous systematic reviews and meta-analyses that used SC as the control group (5, 56, 57). Pecks et al. reported the OR for HDP in OD pregnancies in comparison to SC to be 6.60 (95% CI 4.55–9.57). However, some included studies did not adjust for plurality, potentially leading to an overestimation due to the known risk of multiple pregnancy. Similarly, Masoudian et al. calculated an odds ratio of 4.34 (95% CI 3.10–6.06) with studies that included both singleton and multiple pregnancies. Storgaard et al. reported an odds ratio of 2.45 (95% CI 1.53–1.93) and an odds ratio of 2.95 (95% CI 2.29–3.76) for HDP and preeclampsia, respectively. Since the most recent literature, five other cohort studies were published and included in our analyses (31, 36, 58–60).

In addition to the potential role of CL on maternal circulation, the increased risk of preeclampsia and HDP observed in women who conceived via OD has also been suggested to be a result of a heightened immunologic response between the mother and the allogenic oocyte (61). This was formed on the basis that normal placentation requires the development of immunologic tolerance of the mother and the fetus; studies reporting an increased risk of preeclampsia in primiparous women and after a change in paternity in multiparous women further support this immunologic theory (61, 62). Lashley and colleagues found that among successful and uncomplicated OD pregnancies, there was a higher level of human leukocyte antigen (HLA) matching between mother and fetus in than expected by chance, suggesting the role of HLA gene in the development of preeclampsia (63). However, it is still important to consider other patient factors such as advanced maternal age, which is very common in this patient population and may also play a role to the increased risk of hypertensive disorders.

Strengths and limitations

Our findings were generally consistent with previous literature; however, this study also carries many distinctive strengths. This is the most up-to-date, large-scale meta-analysis (including 78 studies and 7,858,564 pregnancies) studying the association between IVF/ICSI pregnancies and HDP. Strict inclusion and exclusion criteria were employed to focus solely on IVF/ICSI pregnancies and SC (without any fertility treatment) to provide findings that are unique to this ART procedure. Recognizing the inherent risk of HDP in multiple pregnancies, all analyses stratified patients by plurality. Two outcomes, preeclampsia and HDP, were reported separately due to their differences in risk and prognosis. Furthermore, most included studies (89.7%) were of moderate to high quality (Table I, Additional file 4). Finally, all publications in English, Chinese, Portuguese, and French were screened and reviewed to minimize language bias.

However, there were also some limitations. The diagnostic criteria of preeclampsia differ depending on the study period and geographical location (37). The lack of definition for the outcomes of interest among the cohorts (43% of all included studies)

also made it difficult to create a uniform definition for the meta-analysis. This issue was solved by considering the following criteria: if a study used preeclampsia as an outcome without specifying the definition, it was included in analyses for preeclampsia. If a study used terminologies such as “pregnancy-induced hypertension”, “gestational hypertension”, or “hypertensive disorder”, it was only included in analyses for HDP. A high heterogeneity was reported in many pooled analyses, likely due to differences in study populations and geographical areas. Finally, uncontrolled confounders remained to be a concern due to the nature of the study design and could also influence heterogeneity. Some of the included studies did employ a matching method when selecting control subjects, while other studies accounted for potential confounders such as age, parity, medical comorbidities, year of birth, socioeconomic status, ethnic origin, location, and cause of infertility.

Conclusions And Implications

There has been an increasing amount of literature studying the relationship between ART and pregnancy and perinatal outcomes over the past decade, but there is also a lack of clinical practice guidelines for women who conceived through ART (64). Results of our meta-analyses confirmed that IVF/ICSI pregnancies were at high odds of preeclampsia and HDP than SC, irrespective of the plurality. In particular, the odds in FET and OD pregnancies were high. Further population-based research studying different IVF treatment protocols should be considered. Health care providers should be aware of these risks and develop specific care plans and interventions for pregnancies conceived by IVF/ICSI to decrease the incidence of hypertensive complications and subsequently the risks of maternal morbidity and mortality. For example, a systematic review of randomized controlled trials by Henderson et al. suggested that daily low-dose aspirin starting after the first trimester might reduce the risk of preeclampsia (65). The relationship between preeclampsia and ICSI singleton pregnancies remains unclear due to insufficient literature that studies this population. Given that the use of ICSI is gaining popularity over time, more research studying the pregnancy outcomes after ICSI is warranted.

Abbreviations

ART: Assisted reproductive technologies

IVF: In vitro fertilization

ICSI: Intracytoplasmic sperm injection

Fresh ET: Fresh embryo transfer

FET: Frozen embryo transfer

OD: Oocyte donation

HDP: Hypertensive disorders of pregnancy

SC: Spontaneous conception

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

NOS: Newcastle Ottawa Scale

OR: Odds ratio

CL: Corpus luteum

HLA: Human leukocyte antigen

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data underlying this article will be shared on reasonable request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HC: conception of study design, screening, data collection and analysis, manuscript draft and revision. FTSE: conception of study design, screening, data collection, manuscript revision. LG: manuscript revision. MPV: conception of study design, supervision, manuscript revision, and approval of the version to be published. All authors approved the final version of the manuscript.

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Figures

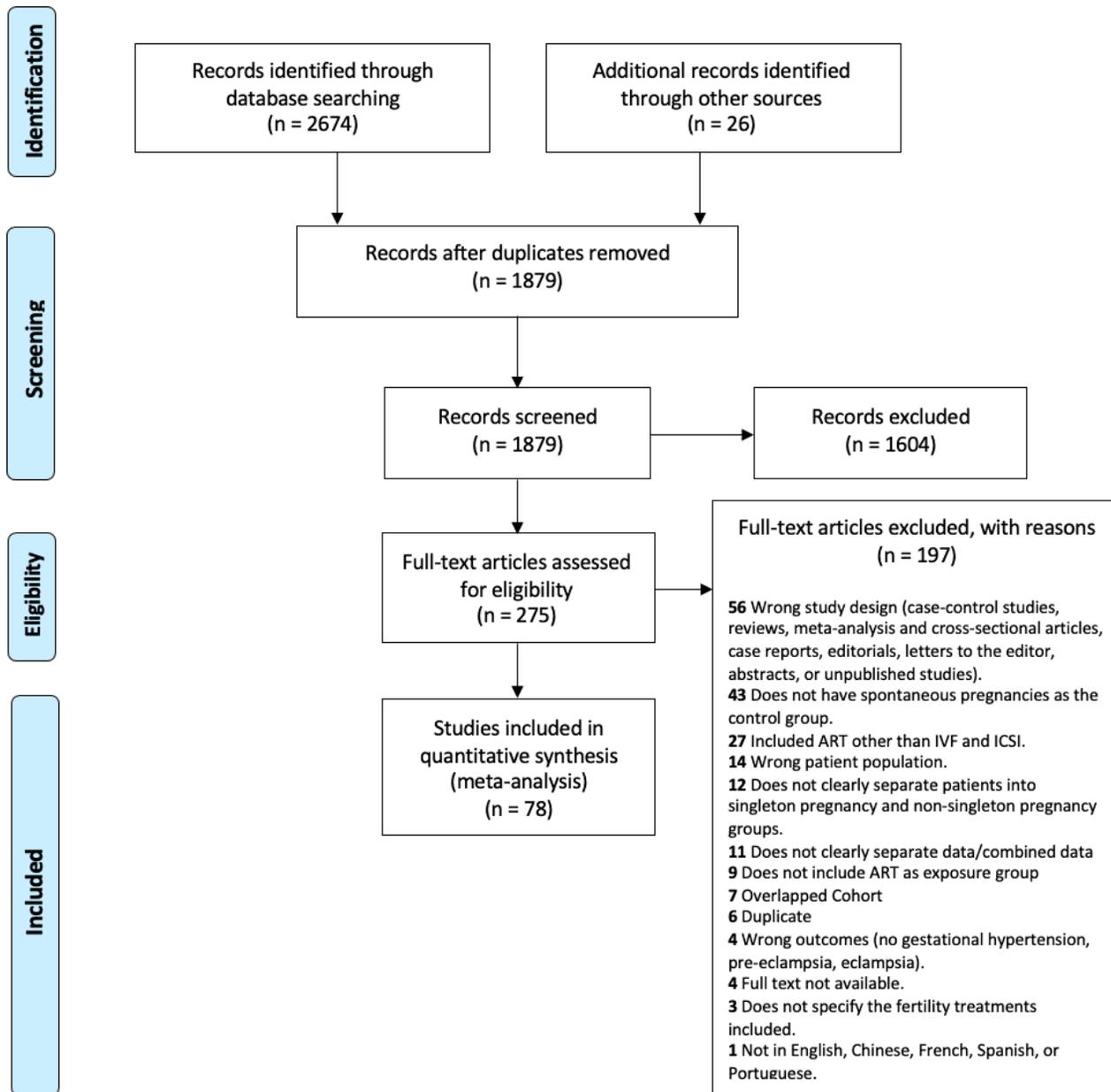
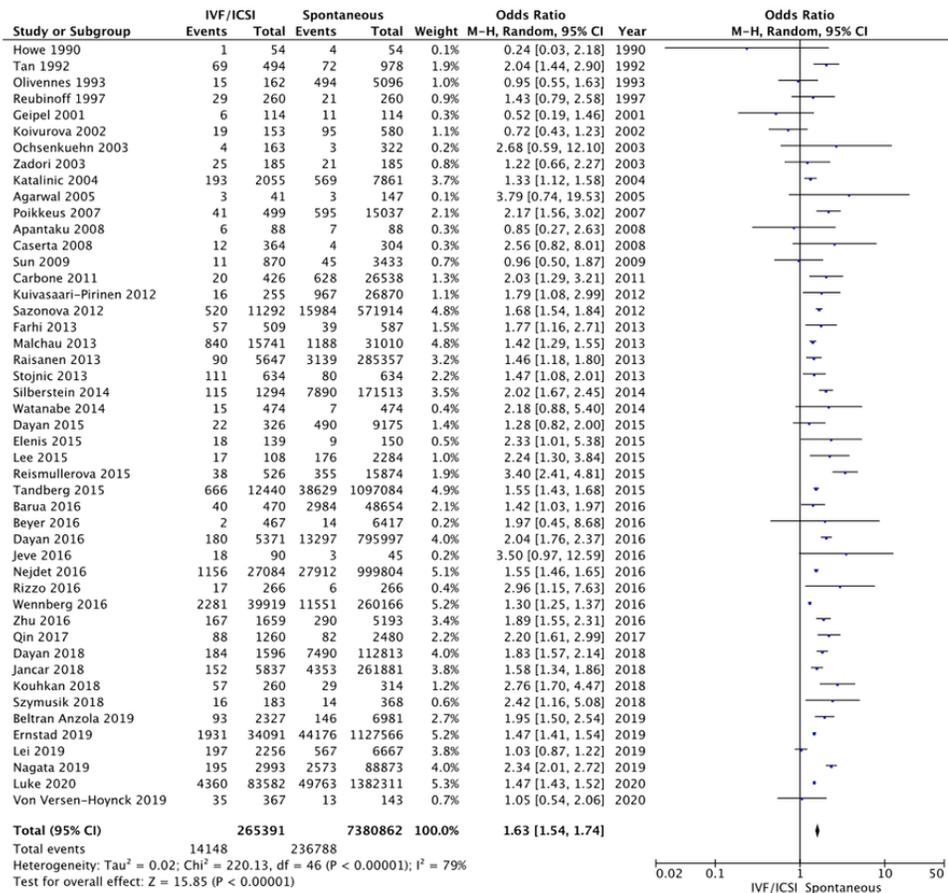


Figure 1

PRISMA Flowchart Flow diagram for study identification and inclusion according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

a) IVF/ICSI singleton pregnancies



b) ICSI singleton pregnancies

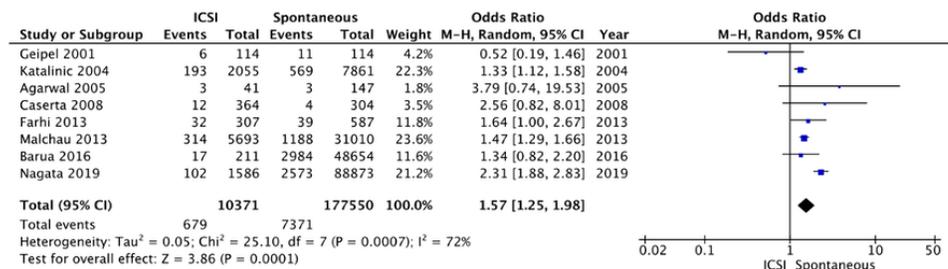
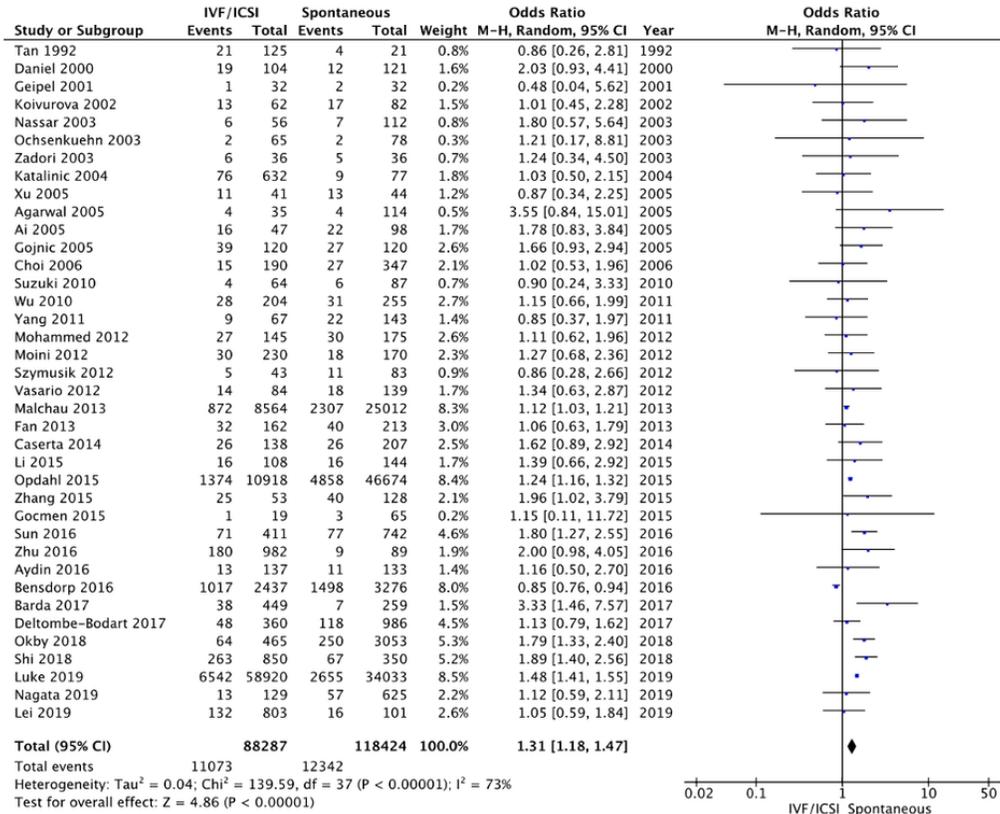


Figure 2

Singleton Pregnancies Meta-analysis Forest plot comparing hypertensive disorders of pregnancy in a) IVF/ICSI singleton pregnancies and b) ICSI singleton pregnancies in comparison to spontaneous pregnancies.

a) IVF/ICSI multiple pregnancies



b) ICSI multiple pregnancies

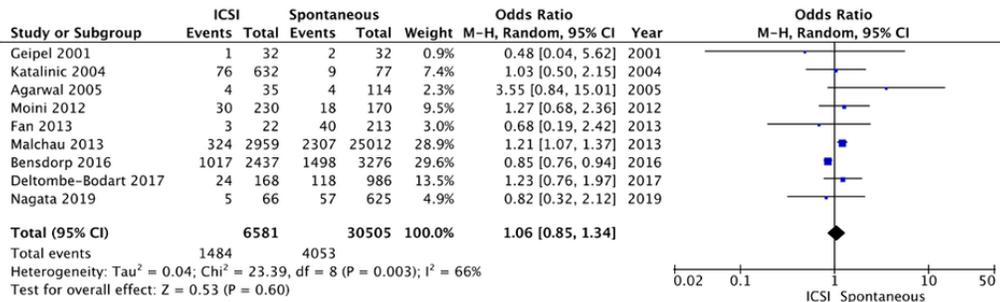
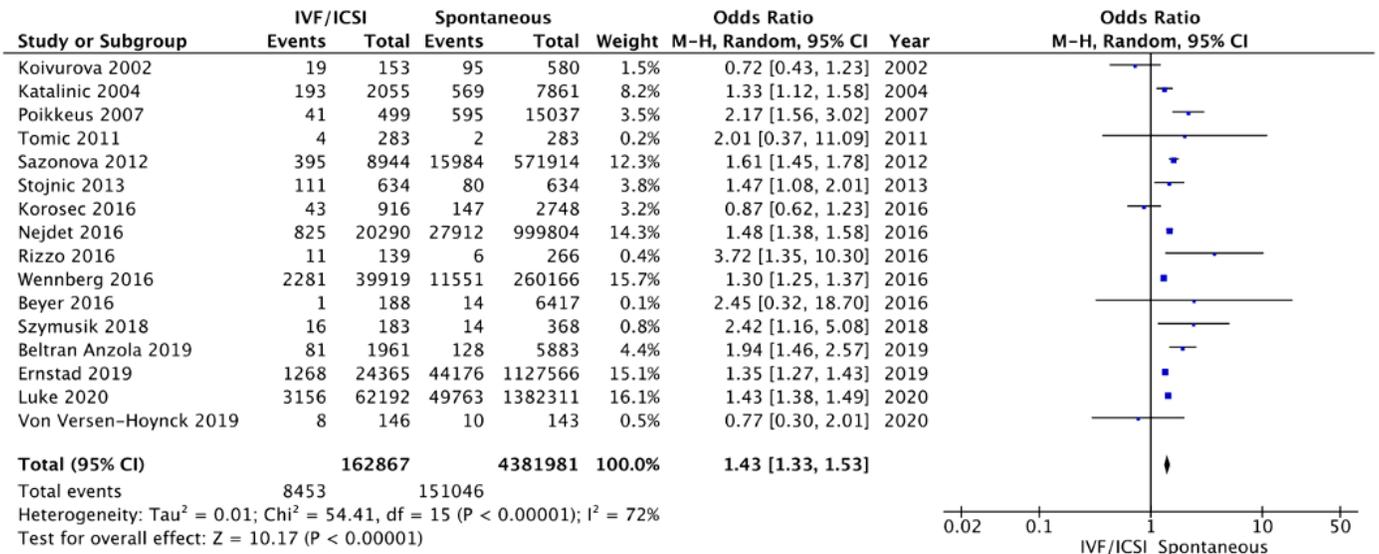


Figure 3

Multiple Pregnancies Meta-analysis Forest plot comparing hypertensive disorders of pregnancy in a) IVF/ICSI multiple pregnancies and b) ICSI multiple pregnancies in comparison to spontaneous pregnancies.

a) Fresh embryo transfer



b) Frozen embryo transfer

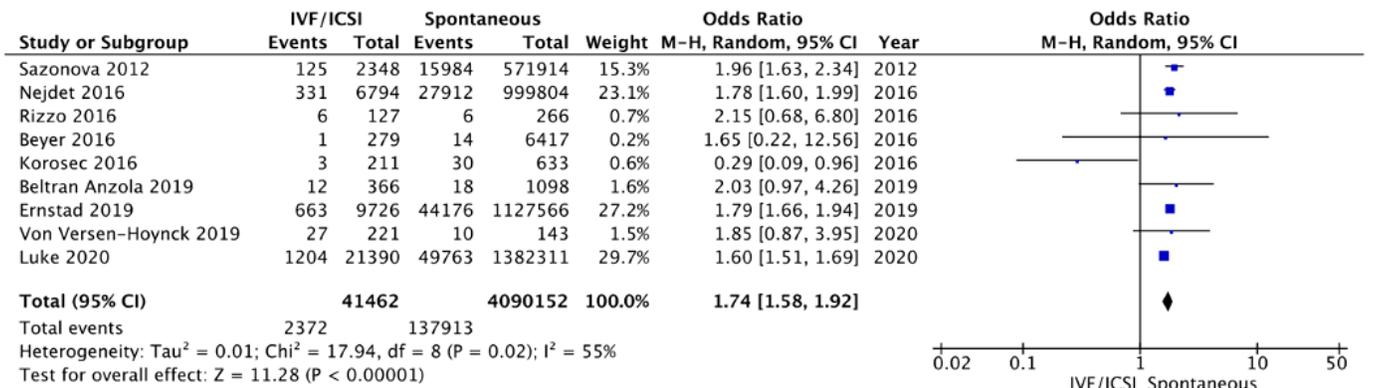
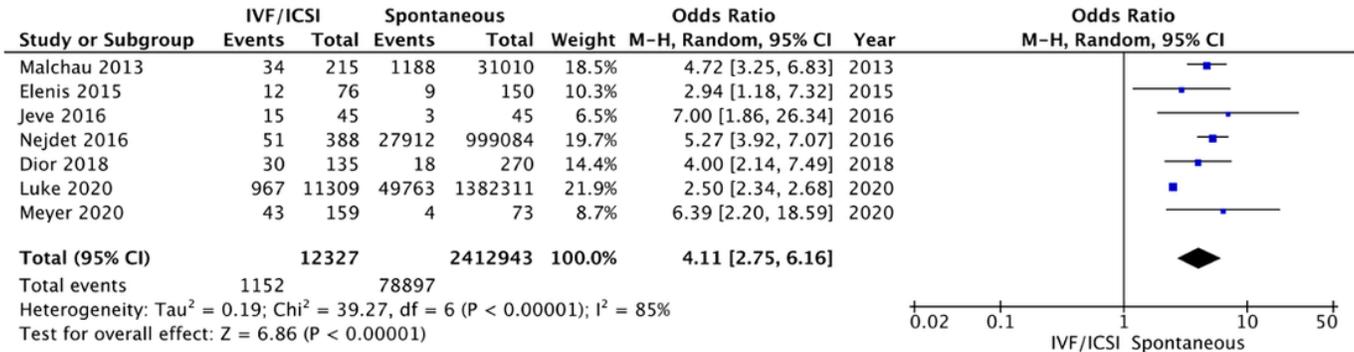


Figure 4

Fresh and Frozen Embryo Transfer Meta-analysis Forest plot comparing hypertensive disorders of pregnancy in singleton pregnancies resulting from a) fresh embryo transfer or b) frozen embryo transfer in comparison to spontaneous pregnancies.

a) Singleton pregnancies



b) Multiple pregnancies

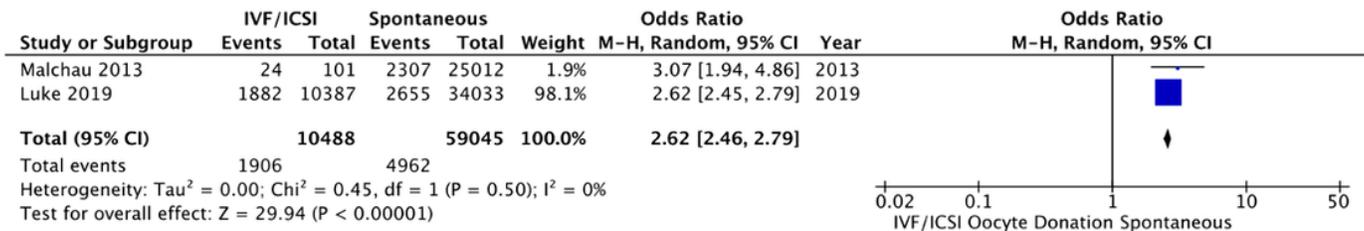


Figure 5

Oocyte Donation Meta-analysis Forest plot comparing hypertensive disorders of pregnancy in a) singleton pregnancies or b) multiple pregnancies resulting from oocyte donation in comparison to spontaneous pregnancies.

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