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Hypertensive disorders of pregnancy after multifetal pregnancy reduction: a systematic review and meta-analysis

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ABSTRACT

Objective: To systematically review the literature on hypertensive disorders of pregnancy (HDP) after multifetal pregnancy reduction (MFPR).

Methods: A comprehensive search in PubMed, Embase, Web of Science, and Scopus was performed. Prospective or retrospective studies reporting on MFPR from triplet or higher-order to twin compared to ongoing (i.e., non-reduced) triplets and/or twins were included. A meta-analysis of the primary outcome HDP was carried out using a random-effects model. Subgroup analyses of gestational hypertension (GH) and preeclampsia (PE) were performed. Risk of bias was assessed using the Newcastle-Ottawa Quality Assessment Scale.

Results: Thirty studies with a total of 9,811 women were included. MFPR from triplet to twin was associated with a lower risk for HDP compared to ongoing triplets (OR 0.55, 95% CI, 0.37–0.83; $p = 0.004$). In a subgroup analysis, the decreased risk of HDP was driven by GH, and PE was no longer significant (OR 0.34, 95% CI, 0.17–0.70; $p = 0.004$ and OR 0.64, 95% CI, 0.38–1.09; $p = 0.10$, respectively). HDP was also significantly lower after MFPR from all higher-order (including triplets) to twin compared to ongoing triplets (OR 0.55, 95% CI, 0.38–0.79; $p = 0.001$). In a subgroup analysis, the decreased risk of HDP was driven by PE, and GH was no longer significant (OR 0.55, 95% CI 0.32–0.92; $p = 0.02$ and OR 0.55, 95% CI 0.28–1.06; $p = 0.08$, respectively). No significant differences in HDP were found in MFPR from triplet or higher-order to twin versus ongoing twins.

Conclusions: MFPR in women with triplet and higher-order multifetal pregnancies decreases the risk of HDP. Twelve women should undergo MFPR to prevent one event of HDP. These data can be used in the decision-making process of MFPR, in which the individual risk factors of HDP can be taken into account.

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Multifetal pregnancy; multifetal pregnancy reduction; hypertensive disorders of pregnancy; meta-analysis

Introduction

Multifetal pregnancies are associated with an increased risk of maternal and perinatal morbidity and mortality compared to singleton pregnancies (1–4). When comparing higher-order multifetal pregnancies (i.e., with three or more fetuses) to twin pregnancies, rates of pregnancy complications are even higher (2,3,5). Maternal risks of multifetal pregnancies include hypertensive disorders of pregnancy (HDP, including gestational hypertension (GH) and preeclampsia (PE)), gestational diabetes , cesarean delivery, and postpartum hemorrhage (6). HDP are described to develop at an earlier gestational age and with higher maternal morbidity comparing multifetal pregnancies with singleton pregnancies (5). Furthermore, HDP are still the leading cause of maternal mortality worldwide, responsible for over 27,800 maternal deaths every year (7). Perinatal risks of multifetal pregnancies are often directly related to perinatal complications including preterm birth and/or very low birth weight (8), with its consequences for the neonate and later in life in terms of neurodevelopmental disorders (9).

The incidence of multifetal pregnancies (twins, triplets, and higher-order pregnancies) has risen remarkably since the 1980s and 1990s, caused by the use of fertility treatments and a higher average maternal age at conception (10,11). Due to primary prevention strategies (12), the

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incidence of multifetal pregnancies has declined and has now stabilized around 34 per 1,000 live births in the United States (13). In 2020, the triplet and higher-order multifetal birth rate was 79.9 per 100,000 births (14).

When a triplet or higher-order multifetal pregnancy occurs, multifetal pregnancy reduction (MFPR) can be considered to reduce the total number of fetuses by one or more, carried out in the first or early-second trimester (15,16). In the counseling for MFPR, the risk of the procedure (i.e., a chance in loss of the entire pregnancy (17,18)) has to be weighed against the possible maternal and perinatal complications associated with a multifetal pregnancy.

Most studies on MFPR show an increase in gestational age at delivery after MFPR compared to ongoing multifetal pregnancies (19–22). Van de Mheen et al. found that MFPR in women with a trichorionic triplet pregnancy is associated with a decreased risk of preterm birth <32 weeks, while risks for pregnancy loss after reduction or preterm birth <24 weeks in ongoing triplet pregnancies are similar (19).

The effect of MFPR on maternal morbidity is not evident. In order to counsel women with multifetal pregnancies on MFPR appropriately, it is important to have a more extensive knowledge on the development of maternal complications during and after pregnancy. Based on recent literature, MFPR from a twin to a singleton pregnancies to improve pregnancy outcomes should not be advised, due to an increased risk of preterm delivery and pregnancy loss (23). Therefore, the objective of this study was to systematically review the literature on HDP and other maternal outcomes after MFPR in women with triplet and higher-order multifetal pregnancies.

Material and methods

Protocol and registration

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (24). The study protocol was registered with the PROSPERO register prior to its commencement (registration number: 344839).

Search strategy

A comprehensive search was performed in the bibliographic databases PubMed, Embase, Web of Science and Scopus from inception to July 6th 2022, in collaboration with a medical librarian (LS). Search terms included controlled terms (MeSH in PubMed and Emtree in Embase) as well as free-text terms. The following terms were used as index terms or free-text words, including synonyms and closely related words: "multiple pregnancies" and "reduction". The search was performed without date or language restrictions. Duplicate articles were excluded by a medical information specialist (LS) using Endnote X20.0.1 (Clarivate^{tm}), following the Amsterdam Efficient Deduplication (AED)-method (25) and the Bramer-method (26). The full search strategies for all databases can be found in the Supplementary Information (Table S1).

Selection process

Two reviewers (PB and JW) independently screened all potentially relevant titles and abstracts for eligibility using Rayyan (27). Studies were included if they met the following criteria: (i) prospective or retrospective studies; (ii) reporting on MFPR from triplets to twins or MFPR from higher-order multifetal pregnancy to twins compared to ongoing (i.e., non-reduced) triplets and/or twins; (ii) featuring HDP (including GH and PE) as an outcome measure. The exclusion criteria were as follows: (i) review articles, case reports, congress abstracts, and letters; (ii) MFPR to singletons; (iii) studies comparing different types of reduction techniques; (iv) studies comparing early versus late reduction; (v) more than 20% of case group (after MFPR) consisting of spontaneous reduction or selective reduction (i.e., reduction for fetal anomaly or complications related to a monochorionic pregnancy (e.g., twin to twin transfusion syndrome (TTTS), twin anemia polycythemia Sequence (TAPS), selective intra uterine growth restriction (sIUGR)); (vi) outcome data published in other language than English. No restrictions regarding chorionicity were made since chorionicity does not appear to substantially influence maternal outcomes (28), except for those with complications related to monochorionic pregnancies. Full texts were obtained if studies appeared to meet the inclusion criteria or in case of uncertainty. All reasons for exclusion were recorded. Reviewing authors were not blinded to the journal titles, study authors, or institutions. Reference and citation lists of the included studies were scanned to ensure literature saturation. Disagreements regarding study selection were resolved by consulting a third author (MB).

Risk of bias in individual studies

Two reviewers (PM and MB) independently assessed the risk of bias using the Newcastle-Ottawa Quality Assessment Scale (NOS) for non-randomized studies (29). Following the manuals of the tools, studies were

scored as either having a "low," "medium," "high," or "unclear" risk of bias.

Outcomes

The primary outcome was HDP, including 1) GH, 2) PE, or 3) both (GH and PE or described as HDP). Secondary outcomes included other maternal outcomes (gestational diabetes (GDM); anemia in pregnancy; cesarean delivery (CD); postpartum hemorrhage (PPH); placental abruption; uterine rupture; HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome; eclampsia; amniotic fluid embolism; pulmonary embolism; maternal intensive care unit admission; maternal death). Definitions of the outcome measures can be found in Table 1.

Data collection process and data items

Data from the included studies were extracted by one author (PB) and checked by another (MB). The following baseline data items were collected for all included studies: country; year of publication; study design; study period; sample sizes; reduction approach (transabdominal/transvaginal); reduction technique (KCL injection/aspiration); gestational age at reduction (weeks); type of HDP (GH/PE/HDP); definition of HDP (if reported). Authors of the accepted studies were contacted for important missing data on baseline characteristics. The following demographic data of all included women were collected if available: maternal age at delivery (years); conception (spontaneous/ovulation induction (OI)/assisted reproductive technology (ART)); parity (nulliparous).

The following primary outcome data were collected for all studies: number and/or proportions of GH/PE/HDP. The following secondary outcome data were extracted and when available the number and/or proportions of the outcome measure were also registered: GDM, anemia, CD, PPH, placental abruption, uterine rupture, HELLP syndrome, eclampsia, amniotic fluid embolism, pulmonary embolism, maternal intensive care unit admission, and maternal death.

Synthesis of results

Outcomes were divided into four groups based on the type of case and control groups of the individual studies: 1) MFPR from triplet to twin pregnancy versus ongoing triplet pregnancies, 2) MFPR from all higher-order (including triplets) to twin pregnancy versus ongoing triplet pregnancies, 3) MFPR from triplet to twin pregnancy versus ongoing twin pregnancies, and 4) MFPR from all higher-order (including triplets) to twin pregnancy versus ongoing twin pregnancies. In the individual studies, the primary outcome HDP were reported as GH, PE, or both (GH and PE or described as HDP). For the primary outcome, we presented outcome data of these HDP subgroups narratively and in summary tables with measures of statistical significance if applicable. Furthermore, a pooled data analysis of the main outcome (HDP) was performed using the Cochrane's Review Manager software Version 5.4 (39). Pooled odds ratios for dichotomous outcomes were calculated using a random-effects model. I^2 test was performed to assess heterogeneity, and a value of less than 50% was considered to represent low heterogeneity. Subgroup analyses were performed based on HDP subgroups (GH, PE, and HDP) as well as types of higher-order multifetal pregnancy in the analyses of MFPR from all higher-order (including triplets) to twin pregnancies compared to triplets and twins (analyses 2 and 4, respectively). For secondary outcome, findings were presented narratively and in summary tables with measures of statistical significance, if applicable, in order to prevent selection bias.

Table 1. Definitions.

Primary outcome	Definition
Gestational hypertension	Persistent *de novo* hypertension that develops at or after 20 weeks of gestation in the absence of features of preeclampsia (30)
Preeclampsia	Gestational hypertension accompanied by one or more of the following new-onset conditions at or after 20 weeks of gestation: 1) proteinuria, 2) other maternal organ dysfunction (acute kidney injury, liver involvement, neurological complications, severe headaches, persistent visual scotomata, or hematological complications), and 3) uteroplacental dysfunction (30)
Secondary outcome	
Gestational diabetes	Any degree of glucose intolerance with onset or first recognition during pregnancy (31)
Anemia in pregnancy	Hemoglobin concentration of less than 11.0 g/dL (32)
Postpartum hemorrhage	Cumulative blood loss of ≥1000 ml within 24 h after childbirth (33)
Placental abruption	Early separation of placenta from the lining of the uterus before completion of the second stage of labor (34)
Uterine rupture	A complete division of all three layers of the uterus (35)
HELLP syndrome	A serious complication in pregnancy characterized by hemolysis, elevated liver enzymes, and low platelet count (36)
Eclampsia	New onset of generalized tonic-clonic seizures in a woman with preeclampsia (37)
Amniotic fluid embolism	Life-threatening obstetric emergency characterized by sudden cardiorespiratory collapse and disseminated intravascular coagulation (38)

Results

Study selection

The literature search generated a total of 5,927 records: 1,421 in PubMed, 1,802 in Embase, 1,315 in Web of Science, and 1,389 in Scopus. Figure 1 shows the selection progress and an overview of the reasons for exclusion. After removing duplicates, 2,507 studies remained. Of them, 598 studies were found to be relevant for full-text assessment. After a full-text assessment, 565 studies were excluded, leaving 27 studies that met the eligibility criteria for this systematic review. One study (40) analyzed early transvaginal MFPR (group 1) and late transabdominal MFPR (group 2) and compared the outcomes of both groups to ongoing twin pregnancies (group 3) separately, rather than a comparison of early versus late reduction. Therefore, we did not exclude this article. In addition, three studies were identified by scanning reference and citation lists, resulting in a total of 30 studies evaluating HDP after MFPR from triplet or higher-order multifetal pregnancy to a twin pregnancy compared to ongoing triplets or twins (40–69).

Study characteristics

Baseline characteristics of all included studies can be found in Table 2. Eleven studies (44,47,50–52,54,55,58–60,66) reported on HDP after MFPR from triplet to twin pregnancy compared to ongoing triplet pregnancies, and three studies (42,61,67) from higher-order multifetal pregnancy to twin pregnancy compared to ongoing triplet pregnancies. Eight studies (45–47,49,53,55,58,62) reported on HDP after MFPR from triplet to twin pregnancy compared to ongoing twin pregnancies, and 16 studies (40–43,45,46,48,56,57,61–65,67–69) from higher-order multifetal pregnancy to twin pregnancy compared to ongoing twin pregnancies. The 30 studies included a total of 9,811 women who met the inclusion criteria: 1,124 (12%) with MFPR from triplet to twin pregnancy and 1,006 (10%) with MFPR from triplet or higher-order multifetal pregnancy to twin pregnancy. Furthermore, there were 877 (9%) women with an ongoing triplet pregnancy and 6,804 (69%) women with an ongoing twin pregnancy in the comparison groups. In 21 (70%) studies, the procedure of MFPR was performed with a transabdominal approach using potassium chloride

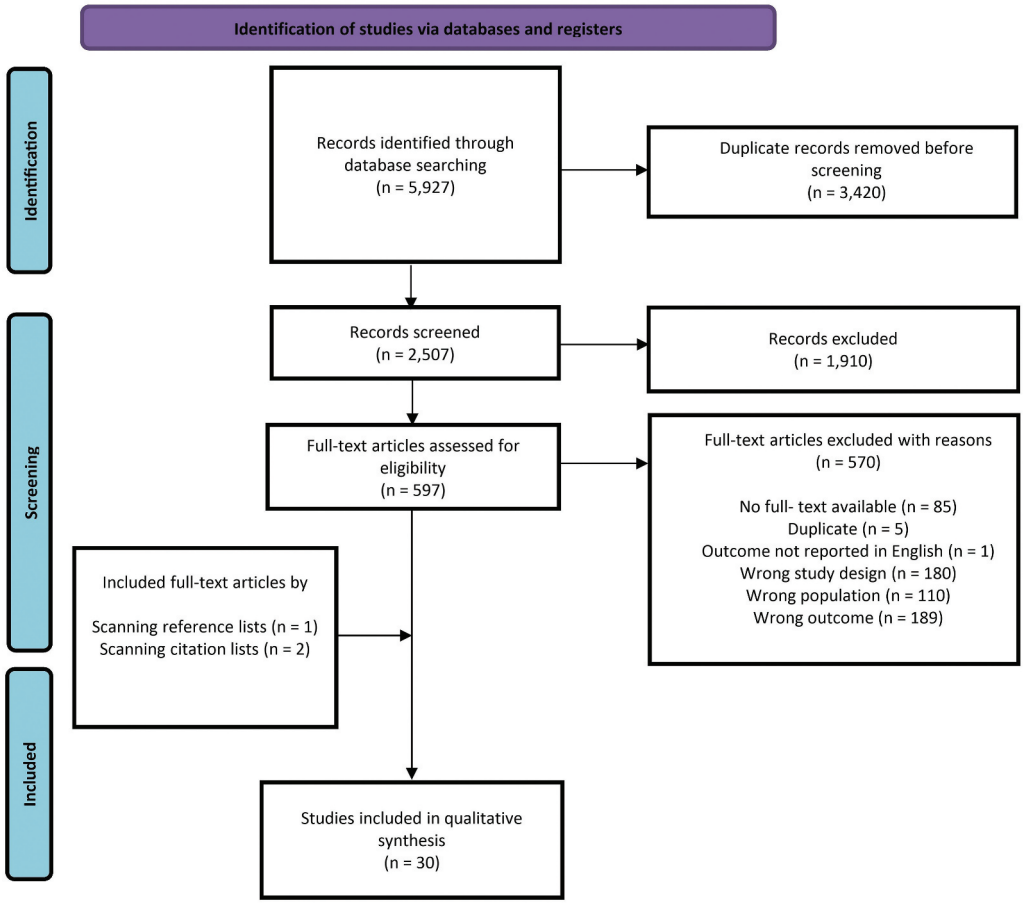

Figure 1. Flowchart depicting article screening and inclusion.

Table 2. Baseline characteristics of the included studies.

Study details					Sample size (total); *n*								
					MFPR		Ongoing pregnancy		Reduction			Primary outcome	
First author	Country	Year	Design	Study period	3 → 2	≥3 → 2	Twin	Triplet	Approach	Method	GA; weeks	HDP	Definition
Alexander (41)	US	1995	RCS	1988–1993	-	32	38	-	TA	KCL	10	PE	NR
Angel (42)	US	1999	RCS	1993–1998	-	16	24	23	TA	KCL	NR	GH	NR
Belogolovkin (43)	US	2007	CCS	2000– 005	-	36	243	-	TA	KCL	10–14	PE	NR
Boulot (44)	France	1993	PCS	1985–1991	32	-	-	48	TV/TA	Aspiration/KCL	8–14	PE	NR
Groutz (45)	Israël	1996	PCS	NR	30	-	30	-	TV	NaCl	10	GH	NR
Haas (46)	Israël	2014	PCS	2005–2011	55	77	78	-	TV	Aspiration	6–8	HDP	NR
Herlihy (47)	US	2017	RCS	2005–2016	42	-	693	43	TA	KCL	12–16	PE	NR
Hwang (48)	Taiwan	2001	RCS	1992–2000	-	54	406	-	TA	KCL	9–12	GH	[a]
Jiang (49)	China	2020	RCS	2010–2019	139	-	149	-	TA	KCL	12–25	HDP	NR
Kadhel (50)	France	1998	RCS	1993–1996	17	-	-	24	TA	KCL	9–11	GH	[b]
Kim (40)	Korea	2019	RCS	2006–2018		212	157	-	TV/TA	Aspiration/KCL	6–8/11–17	HDP	NR
Lee (51)	Korea	2022	RCS	2006–2018	327	-	-	225	TV/TA	Aspiration/KCL	8–10/10–14	PE	[c]
Lipitz (52)	Israël	1994	PCS	1984–1992	31	-	-	84	TA	KCL	9	GH	NR
Lipitz (53)	Israël	1996	RCS	1989–1993	43	-	134	-	TA	KCL	9	GH	NR
Liu (54)	China	2022	RCS	2015–2020	141	-	-	41	TV	Aspiration	6–8	GH	NR
Macones (55)	US	1993	RCS	1988–1992	47	-	63	14	TA	KCL	9–12	HDP	NR
Mostajeran (56)	Iran	2006	PCS	2003–2005	-	30	30	-	TA	KCL	10–13	GH	NR
Nevo (57)	Israël	2003	CCS	1989–1997	-	64	64	-	TV/TA	Aspiration/KCL	7–8/9–11	PE	NR
Okyay (58)	Turkey	2014	RCS	2003–2012	43	-	233	65	TA	KCL	11–14	PE	[d]
Porreco (59)	US	1991	PCS	1991	13	-	-	11	TA	KCL	10–11	GH	NR
Raval (60)	US	2015	RCS	1999–2009	30	-	-	102	TA	KCL	10–14	PE	NR
Razaz (61)	Canada	2017	RCS	2009–2013		45	3340	40	NR	NR	NR	GH	NR
Selam (62)	US	1999	RCS	1986–1997	49	77	140	-	TA	KCL	10–13	GH	[e]
Seo (63)	Korea	2003	RCS	1995–2002	-	43	264	-	TV	KCL	6–9	PE	NR
Silver (64)	US	1997	CCS	1990–1994	-	18	108	-	TA	KCL	13	PE	NR
Singh (65)	India	2021	PCS	2018–2020	-	64	100	-	TA	KCL	11–13	HDP	NR
Sivan (66)	Israël	2002	RCS	1994–1998	85	-	-	103	TA	KCL	10–14	PE	[f]
Smith-Levitin (67)	US	1996	RCS	1990–1994	-	59	88	54	TA	KCL	10–12	PE	NR
Wang (68)	China	2016	RCS	2002–2012	-	130	140	-	TA	KCL	12–25	HDP	NR
Yuce (69)	Turkey	2016	RCS	2007–2014	-	49	282	-	TA	KCL	10–13	PE	NR

ACOG, American College of Obstetricians and Gynecologists; CCS, case-control study; GA, gestational age; GH, gestational hypertension; HDP, hypertensive disorders of pregnancy; KCL, potassium chloride; MFPR, multifetal pregnancy reduction; n, number; NR, not reported; PCS, prospective cohort study; PE, preeclampsia; RCS, retrospective cohort study; US, United States; SD, standard deviation; TA, transabdominal; TV, transvaginal.

[a]According to standard criteria of the American College of Obstetricians and Gynecologists (ACOG) (74); [b]Systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg; [c]High blood pressure (≥140/90 mmHg) and one or more of the following complications after 20 weeks of pregnancy: proteinuria (≥300 mg/24 h, or urine protein: creatinine ratio ≥ 0.3, or dipstick 1+ persistently), thrombocytopenia (platelet count < 100 000/μL), renal insufficiency (creatinine level >1.1 mg/dL or doubling of baseline), impaired liver function, new onset of headaches or visual disturbances; [d]Hypertension (systolic blood pressure ≥140 mmHg after 24 weeks gestation) plus proteinuria (urine protein concentration ≥300 mg in a 24-h urine sample) (75); [e]Blood pressure ≥ 140/90 mmHg on two occasions within a 6-hour interval or an increase of >30 mmHg systolic or >15 mmHg diastolic above the first-trimester blood pressure; [f]Blood pressure ≥ 140/90 mmHg on two occasions within a 6-hour interval or an increase of >30 mmHg systolic or >15 mmHg diastolic above the first-trimester blood pressure, with proteinuria >300 mg/24 h or weight gain > 5 lb in ≤1 week, as defined by the ACOG criteria (74).

(KCL), eight (27%) studies used other methods (Table 2), or a combination of transabdominal KCL injection and other methods depending on the gestational age at reduction. In one study (3%), the method of reduction was not reported. Six (20%) studies described their definition of diagnosis of either GH, PE, or HDP.

Baseline characteristics of included women

Demographic baseline characteristics are presented in Table 3. Of all studies, 24 (80%) reported on maternal age of the included women, 28 (93%) on conception methods, and 22 (73%) on the amount of nulliparous women. No differences in maternal age were seen in women with MFPR from triplet or higher-order multifetal pregnancy to twins compared to women with ongoing triplets. In six studies (43,46,47,65,69) a significant higher maternal age was found in women with MFPR from triplet or higher-order multifetal pregnancy to twins compared to women with ongoing twins. In general, women in the MFPR groups were substantially more likely to have used OI or ART than women with ongoing triplet or twin pregnancies. No substantial trend was seen in the amount of nulliparous women within groups.

Risk of bias within studies

The results of our risk of bias assessment using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies and case–control studies can be found in Table S2. The risk of bias was "low" in four studies and "moderate" in the remaining 27 studies.

Table 3. Demographic baseline characteristics of all the included studies.

First author	Study groups	Maternal age in years; mean ± SD	Conception methods, %	Nulliparous, % or mean ± SD
Alexander (41)	MFPR ≥3→2, ongoing twin	30.6 vs. 31.2 ($p = 0.498$) (SD = NR)	Spontaneous, OI, IVF, GIFT	75 vs. 75 (p = NS)
Angel (42)	MFPR ≥3→2, ongoing twin, ongoing triplet	32.3 ± 0.3 vs. 32.7 ± 1.0 vs. 32.0 ± 0.9 (p = NS)	Spontaneous, OI, IVF, GIFT	84 vs. 46 vs. 84 (p = NS)
Belogolovkin (43)	MFPR ≥3→2, ongoing twin	36.7 ± 4.7 vs. 33.2 ± 6.3 ($p = 0.002$)	ART (97 vs. 56; $p < 0.0001$)	25 vs. 29 ($p = 0.47$)
Boulot (44)	MFPR 3→2, ongoing triplet	32.6 ± 4 vs. 30.4 ± 3.7 ($p = 0.13$)	Spontaneous (8.3 vs. 0), OI (1.4 vs. 15.6), IVF (79.2 vs. 81.3), GIFT (2.1 vs. 0)	84.4 vs. 85.4 (p = NS)
Groutz (45)	MFPR 3→2, ongoing twin	31.8 ± 4.6 vs. 30.9 ± 3.9 (p = NR)	Spontaneous (0 vs. 100), OI or ART (100 vs. 0)	60 vs. 60 (p = NS)
Haas (46)	MFPR 3→2, MFPR ≥ 3→2, ongoing twin	35.1 ± 6.1 vs. 31.7 ± 4.2 ($p < 0.01$)[a]; 33.6 vs. 31.7 ± 4.2 ($p = 0.02$)[b]	Spontaneous, OI, IVF, egg donation	0.49 vs. 0.52 (p = NS)[b]
Herlihy (47)	MFPR 3→2, ongoing twin, ongoing triplet	36.3 ± 4.2 vs. 34.4 ± 6.5 vs. 29.7 ± 5.5 ($p < 0.001$)	Spontaneous, IVF (69 vs. 66.2 vs. 51.2; $p = 0.116$)	73.8 vs. 62.3 vs. 44.2 ($p = 0.016$)
Hwang (48)	MFPR ≥3→2, ongoing twin	32.0 ± 3.6 vs. 29.0 ± 4.4 ($p < 0.01$)	Spontaneous (0 vs. 47; $p < 0.01$), OI (7 vs. 39; $p < 0.01$), IVF (92 vs. 14; $p < 0.01$)	NR
Jiang (49)	MFPR 3→2, ongoing twin	NR	NR	NR
Kadhel (50)	MFPR 3→2, ongoing triplet	31.7 ± 5.8 vs. 30.8 ± 4.2 (p = NS)	Spontaneous, ART (100 vs. 75)	82.3 vs. 58.3 (p = NS)
Kim (40)	MFPR ≥3→2, ongoing twin	33.0 ± 3.5[c] vs. 32.5 ± 3.7[d] vs. 33.9 ± 3.0 ($p = 0.011$)	IUI (10.5c vs. 10.2d vs. 12.7; $p = 0.778$), IVF/ICSI (89.5c vs. 89.8d vs. 86.6; $p = 0.673$)	86.3 vs. 84.7 vs. 9.4 ($p = 0.392$)
Lee (51)	MFPR 3→2, ongoing triplet	33.6 ± 3.9 vs. 33.2 ± 3.4 ($p = 0.064$)	Spontaneous (3.7 vs. 4.0), OI (15 vs. 41.8), IVF (81.3 vs. 54.2) ($p < 0.001$)	85.6 vs. 85.8 ($p = 0.532$)
Lipitz (52)	MFPR 3→2, ongoing triplet	27 ± 5 vs. 28 ± 6 (p = NS)	Spontaneous (2.9 vs. 6.6), OI (47 vs. 67.8), IVF (50 vs. 25.4; $p < .01$)	73.5 vs. 6.3 (p = NS)
Lipitz (53)	MFPR 3→2, ongoing twin	27 ± 5.1 vs. 27 ± 6.0 (p = NS)	Spontaneous (0 vs. 4.2; $p < 0.001$), OI (46.5 vs. 36.6), IVF (53.5 vs. 23.2)	69.7 vs. 64.1 (p = NS)
Liu (54)	MFPR 3→2, ongoing triplet	30.3 ± 4.4 vs. 29.2 ± 4.4 (p = NS)[e]; 32.2 ± 4.6 vs. 32.0 ± 3.5 (p = NS)[f]	IVF/ICSI	NR
Macones (55)	MFPR 3→2, ongoing twin, ongoing triplet	32.2 ± 3.0 vs. 29 ± 5.2 vs. 30 ± 5.1 (p = NS)	NR	0.5 vs. 0.9 vs. 0.6 (p = NS)
Mostajeran (56)	MFPR ≥3→2, ongoing twin	NR	IVF/ICSI	NR
Nevo (57)	MFPR ≥3→2, ongoing twin	NR	Spontaneous (1.6 vs. 67.2; p = sign.), OI (39.1 vs. 1.9; p = sign.), IVF (59.4 vs. 21.9; p = sign.)	NR
Okyay (58)	MFPR 3→2, ongoing twin, ongoing triplet	29.6 ± 4.8 vs 30.1 ± 5.3 vs 28.9 ± 4.5 (p = NS)	OI (0 vs. 9.9 vs. 6.2), IVF (100 vs. 9.1 vs. 93.8; $p = 0.103$)	93 vs. 81.5 vs. 83.1 (p = NS)
Porreco (59)	MFPR 3→2, ongoing triplet	NR	OI (15.4 vs. 72.7), IVF (61.5 vs. 27.3), GIFT (23.1 vs. 0)	NR
Raval (60)	MFPR 3→2, ongoing triplet	34 ± 4.1 vs. 32.5 ± 4.3 ($p = 0.094$)	Spontaneous, IVF (100 vs. 67.6; $p = 0.002$)	1.13 vs. 1.23 ($p = 0.755$)
Razaz (61)	MFPR ≥3→2, ongoing twin, ongoing triplet	Categorized (n; %) <35 (37.8 vs. 63.6 vs. 57), 35–39 (44.4 vs. 26.9 vs. 30), ≥40 (17.8 vs. 9.6 vs. 12.5)	Spontaneous, ART (88.9 vs. 35.5 vs. 65.0)	66.7 vs. 51.8 vs. 65 (p = NS)
Selam (62)	MFPR 3→2, MFPR ≥ 3→2, ongoing twin	36.1 ± 5.6 vs. 34.7 ± 5.4 vs. 33.8 ± 5.5 (p = NS)	Spontaneous, infertility treatment including IVF (63.3 vs. 59.7 vs. 31.4; p = sign.)	71.4 vs. 71.4 vs. 62.9 (p = NS)
Seo (63)	MFPR ≥3→2, ongoing twin	30.1 ± 3.1 vs. 28.4 ± 4.0 (p = NS)	Spontaneous (0 vs. 100), ART (100 vs. 0)	NR
Silver (64)	MFPR ≥3→2, ongoing twin	32.4 ± 3.2 vs. 30.2 ± 4.9[g] vs. 34.4 ± 4.9[h] (p = NR)	OI (17 vs. 0 vs. 56), IVF (17vs. 0 vs. 24), GIFT (66 vs. 0 vs. 20) ($p = 0.01$)	50 vs. 33 vs. 20 (p = NR)
Singh (65)	MFPR ≥3→2, ongoing twin	37.0 ± 6.8 v. 32.5 ± 4.2 ($p < 0.001$)	Spontaneous (9.4 vs. 25), OI (15.6 vs. 11.0), IVF (75 vs. 64) ($p = 0.146$)	.18±.41 vs. .22 ± .55 ($p < .001$)

(*Continued*)

Table 3. (Continued).

First author	Study groups	Maternal age in years; mean ± SD	Conception methods, %	Nulliparous, % or mean ± SD
Sivan (66)	MFPR 3→2, ongoing triplet	29.3 vs. 29.2 ($p = 0.9$) (SD = NR)	Spontaneous, OI (37.6 vs. 39.8; $p = 0.9$), IVF (61.2 vs. 54.4; $p = 0.4$)	1.5±.7 vs. 1.6 ± 1.1 ($p = 0.8$)
Smith-Levitin (67)	MFPR ≥3→2, ongoing twin, ongoing triplet	NR	IVF (89.3 vs. 97.6 vs. 87), other ART	75.9 vs. 82.7 vs. 84 (p = NS)
Wang (68)	MFPR ≥3→2, ongoing twin	NR	ART	NR
Yuce (69)	MFPR ≥3→2, ongoing twin	33.1 ± 2.4 vs. 31.1 ± 6.1[i] vs. 29.6 ± 5.2[j] ($p = 0.008$)	Spontaneous (NR vs. 100 vs 0), IVF (NR vs. 0 vs. 100)	0.16 ± 0–1 vs. 0.56 ± 0–3 vs. 0.05 ± 0–1 ($p < 0.001$)

ART, assisted reproductive technology; GIFT, gamete intrafallopian transfer; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; MFPR, multifetal pregnancy reduction; NR, not reported; NS, not significant; OI, ovulation induction; SD, standard deviation; sign., significant; vs., versus; yrs, years.

[a]MFPR 3→2 versus ongoing twin; [b]MFPR ≥3→2 versus ongoing twin; [c]Early transvaginal embryo reduction (ER); [d]Late transvaginal fetal reduction (FR); [e]DCTA reduction to twin versus DCTA-expectant management[f]TCTA reduction to twin versus TCTA-expectant management; [g]Spontaneously conceived twins; [h]Twins conceived through infertility therapy; [i]Spontaneously conceived twins; [j]IVF conceived twins.

Results of individual studies

HDP after MFPR from triplet and higher-order multifetal pregnancy to twin pregnancy versus ongoing triplet pregnancies

Results of individual studies comparing GH, PE, or HDP after MFPR from triplet or higher-order to twin pregnancy versus ongoing triplet pregnancies can be found in Table S3. MFPR from triplet to twin pregnancy was associated with a lower risk for HDP compared to ongoing triplet pregnancies (Figure 2), with a corresponding odds ratio (OR) of 0.55 (95% confidence interval (CI), 0.37–0.83; $p = 0.004$; $I^2 = 23\%$). In a subgroup analysis of PE, the difference was no longer significant (Figure S1, OR 0.64, 95% CI, 0.38–1.09; $p = 0.10$; $I^2 = 39\%$), while GH remained significant lower in MFPR from triplet to twin compared to ongoing triplets (Figure S1, OR 0.34,95% CI, 0.17–0.70; $p = 0.004$; $I^2 = 0\%$). HDP was also significantly lower after MFPR from all higher-order (including triplets) to twin pregnancy compared to ongoing triplet pregnancies (Figure 3, OR 0.55, 95% CI, 0.38–0.79; $p = 0.001$; $I^2 = 29\%$). In a subgroup analysis of HDP after MFPR from all higher-order to twin pregnancy compared to ongoing triplets, without studies including MFPR from triplet to twin only, the difference in HDP was no longer significant (Figure 3, OR 0.58, 95% CI, 0.20–1.70; $p = 0.32$; $I^2 = 62\%$). Also, in a subgroup analysis of GH, the difference was no longer significant (Figure S2, OR 0.55, 95% CI, 0.28–1.06; $p = 0.08$; $I^2 = 21\%$). The subgroup analysis of PE was consistent with the main analysis (Figure S2) since PE was significantly decreased in women after MFPR from all higher-order to twin pregnancy versus ongoing triplet pregnancies (Figure S2, OR 0.55, 95% CI, 0.32–0.92; $p = 0.02$; $I^2 = 50\%$).

HDP after MFPR from triplet and higher-order multifetal pregnancy to twin pregnancy versus ongoing twin pregnancies

Results of individual studies comparing GH, PE, or HDP after MFPR from triplet or higher-order to twin pregnancy versus ongoing twin pregnancies can be found in Table S4. There were no significant differences in HDP when comparing MFPR from triplet to twin pregnancy and ongoing twin pregnancies (Figure S3, OR 1.28, 95% CI, 0.79–2.07; $p = 0.32$; $I^2 = 23\%$). Also, no significant differences in HDP were found after MFPR from all higher-order to twin pregnancy (including triplets) versus ongoing twin pregnancies (Figure S4, OR 1.06, 95% CI, 0.85–1.33; $p = 0.59$; $I^2 = 0\%$). For the comparison of MFPR from triplet to twin versus ongoing twin pregnancies, the analyses of subgroups of HDP (GH, PE, and HDP) were consistent with the main analysis (Figure S5). In a subgroup analysis, GH was significantly higher in women with twins after MFPR from triplet or higher-order multifetal pregnancies compared to women with ongoing twins (Figure S6, OR 1.67, 95% CI, 1.08–2.57; $p = 0.02$; $I^2 = 0\%$).

Other maternal outcomes

Table 4 provides detailed information with regard to other maternal outcomes. Of all studies, 21 (70%) reported on gestational diabetes (GDM), 17 (57%) on cesarean delivery (CD), 4 (13%) on postpartum hemorrhage (PPH), and 7 (23%) on placental abruption. Most studies did not find a significant difference in GDM in women after MFPR from triplet or higher-order pregnancy to twin pregnancy compared to women with either ongoing triplet or twin pregnancies (42,43,45–47,49,51,55,57,58,67,68). One study (63) showed a significantly higher risk for GDM in women after MFPR

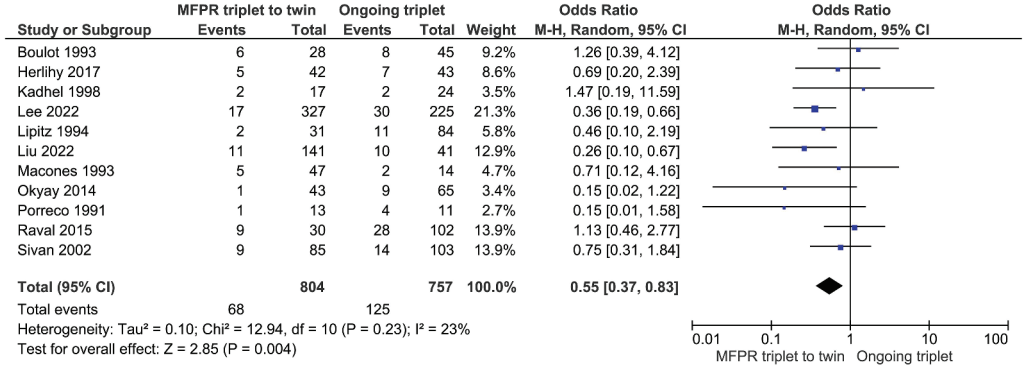

Figure 2. HDP after MFPR from triplet to twin pregnancy versus ongoing triplet pregnancies.

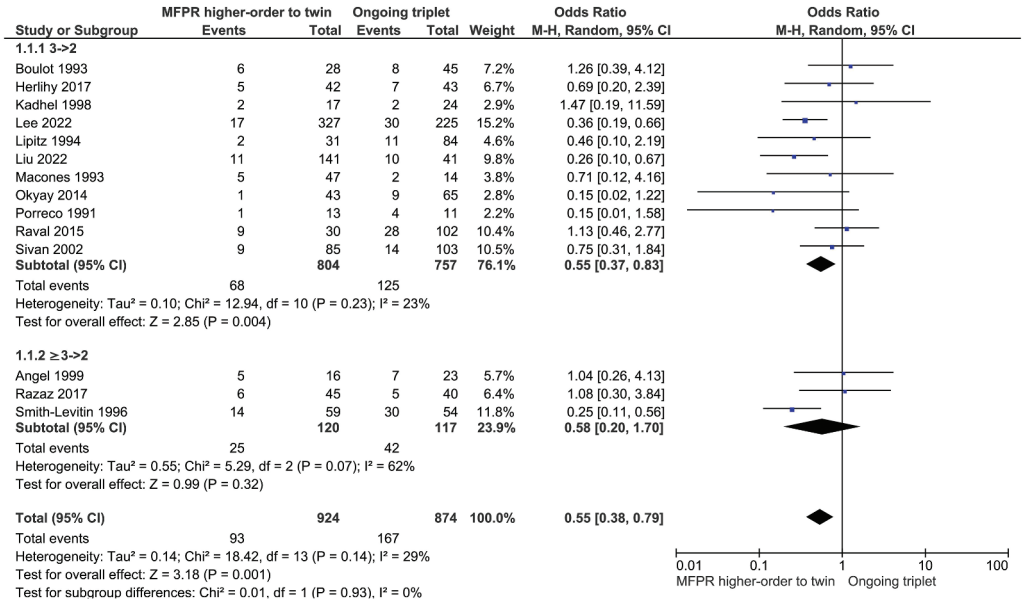

Figure 3. HDP after MFPR from all higher-order to twin pregnancy versus ongoing triplet pregnancies.

from triplet to twin pregnancy versus ongoing twin pregnancies ($p = 0.022$). Two studies (60,66) reported a significant decrease in risk for GDM after MFPR from triplet to twin versus ongoing triplet pregnancies. Kim et al. (40) reported that women with twin pregnancies after MFPR from higher-order pregnancy (with early transvaginal method) have lower risk for GDM compared to women with ongoing twin pregnancies (OR 2.33, 95% CI, 1.06–5.10; $p = 0.034$).

A lower incidence of CD in women with twin pregnancies after MFPR from triplet or higher-order pregnancy compared to women with ongoing triplet pregnancies was found in most studies (44,47,50,52,58,59,61,66), however only three studies (50,52,66) reported a significant difference. Two studies (58,62) found a significantly higher incidence of CD among women with a twin pregnancy after MFPR compared to women with ongoing twin pregnancies. Of the three studies reporting on PPH (47,51,62), none showed a significant difference in PPH in women after MFPR versus women with ongoing twin or triplet pregnancies. In the studies reporting on placental abruption (43,56,58–60,62,64), no significant differences were found within the groups. A limited number of studies focused on HELLP syndrome (44,69) or pulmonary embolism (44), and none of these reported significant differences in outcome within the groups. No studies have been reported on anemia, uterine rupture, eclampsia, amniotic fluid embolism, maternal intensive care unit admission, or maternal death.

Discussion

The results of this systematic review and meta-analysis indicate that women after MFPR from a triplet or higher-order multifetal pregnancy to a twin pregnancy have a significantly lower risk for HDP compared to women with ongoing triplet pregnancies. For MFPR from triplet to twin, this result is driven by GH. For MFPR from higher-order to twin, this result is driven by PE. Furthermore, this meta-analysis found that women with twins after MFPR (from triplet or higher-order pregnancy) have a similar risk for HDP compared to women with ongoing twin pregnancies. Based on these results, MFPR in women with triplet and higher-order multifetal pregnancies can be considered, and might result in a decrease in the occurrence of HDP, with potentially important consequences for other pregnancy complications such as (iatrogenic) preterm birth. To our knowledge, this is the first systematic review to focus exclusively on HDP after MFPR, providing an evaluation of all evidence currently available.

In terms of other maternal outcomes, this systematic review found that MFPR from triplet or higher-order multifetal pregnancy to a twin pregnancy compared to ongoing triplet or twin pregnancies does not seem to be associated with altered risk for GDM, PPH, HELLP syndrome, and pulmonary embolism. As expected, incidence of CD is lower in women after MFPR from triplet or higher-order multifetal pregnancy to a twin pregnancy compared to ongoing triplet pregnancies.

Table 4. Other maternal outcomes.

Comparison/ study	GDM; *n* (%)	CD; *n* (%)	PPH; *n* (%)	Placental abruption; *n* (%)	HELLP; *n* (%)	Pulm. embolism; *n* (%)
MFPR 3→2 vs. ongoing triplet						
Boulot (43)	NR	10/38 (26) vs. 44/45 (98) (p = NR)	0/32 (0) vs. 1/48 (2) (p = NR)	NR	0/32 (0) vs. 1/48 (2) (p = NR)	0/32 (0) vs. 2/48 (4) (p = NR)
Herlihy (46)	4/42 (10) vs. 6/43 (14) (aOR 0.58 (0.11–3.00))	29/42 (69) vs. 37/43 (86) (aOR 0.25 (0.06–0.94))	3/42 (7) vs. 1/43 (2) (aOR 2.62 (0.20–21.3))[a]	NR	NR	NR
Kadhel (49)	NR	4/17 (24) vs. 17/24 (71) (p < 0.01)	NR	NR	NR	NR
Lee (50)	11/327 (3) vs. 14/225 (6) (aOR 0.48 (0.20–1.12; p = 0.1))	NR	15/327 (5) vs. 5/225 (2) (aOR 1.84 (0.63–5.36; p = 0.261))	NR	NR	NR
Lipitz (1994) (51)	NR	18/31 (58) vs. 78/84 (93) (p < 0.001)	NR	NR	NR	NR
Liu (53)[b]	3/16 (19) vs. 4/24 (17) (p = NR)	NR	NR	NR	NR	NR
Liu (53)[c]	5/125 (4) vs. 3/17 (18) (p = NR)	NR	NR	NR	NR	NR
Macones (54)	1/45 (2) vs. 0/14 (0) (p = NS)	NR	NR	NR	NR	NR
Okyay (57)	2/43 (5) vs. 6/65 (9) (p = NS)	36/43 (84) vs. 58/65 (89) (p = NR)	NR	0/43 (0) vs. 1/65 (2) (p = NS)	NR	NR
Porreco (58)	1/13 (8) vs. 0/11 (0) (p = NR)	8/13 (62) vs. 11/11 (100) (p = NR)	NR	1/13 (8) vs. 0/11 (0) (p = NR)	NR	NR
Raval (59)	1/30 (3) vs. 23/102 (23) (p = 0.015)	NR	NR	0/30 (0) vs. 2/102 (2) (p = 1.0)	NR	NR
Sivan (65)	5/85 (6) vs. 23/103 (22) (p = 0.003)	59/85 (69) vs. 89/103 (86) (p < 0.001)	NR	NR	NR	NR
MFPR ≥3→2 vs. ongoing triplet						
Angel (41)	1/16 (6) vs. 3/23 (13) (p = NS)	NR	NR	NR	NR	NR
Razaz (60)	13/45 (29) vs. 8/40 (20) (p = NR)	31/45 (69) vs. 35/40 (88) (p = NR)	NR	NR	NR	NR
Smith-Levitin (66)	3/59 (5) vs. 4/54 (7) (p = NS)	NR	NR	NR	NR	NR
MFPR 3→2 vs. ongoing twin						
Groutz (44)	Incidence of GDM similar between groups	21/30 (70) vs. 17/30 (57) (p = NS)	NR	NR	NR	NR
Haas (45)	8/55 (15) vs. 11/78 (14) (p = NS)	NR	NR	NR	NR	NR
Herlihy (46)	4/42 (10) vs. 64/693 (9) (aOR 0.92 (0.31–2.67))	29/42 (69) vs. 433/693 (62) (aOR 1.10 (0.54–2.16))	3/42 (7) vs. 34/693 (5) (aOR 1.43 (0.42–4.90))[a]	NR	NR	NR
Jiang (48)	4/139 (3) vs. 3/149 (2) (p = 0.425)	NR	NR	NR	NR	NR
Lipitz (1996) (52)	NR	25/43 (58) vs. 65/134 (49) (RR 1.20 (0.88–1.63))	NR	NR	NR	NR
Macones (54)	1/47 (2) vs. 1/63 (2) (p = NS)	NR	NR	NR	NR	NR
Okyay (57)	2/43 (5) vs. 16/233 (7) (p = NS)	36/43 (84) vs. 137/233 (59) (p < 0.001)	NR	0/43 (0) vs. 2/233 (1) (p = NS)	NR	NR
Selam (61)	NR	34/49 (69) vs. 73/140 (52) (p < 0.05)	1/49 (2) vs. 4/140 (3) (p = NS)	3/49 (6) vs. 2/140 (1) (p = NS)	NR	NR
MFPR ≥3→2 vs. ongoing twin						
Alexander (40)	2/32 (6) vs. 4/38 (11) (p = NR)	23/32 (71) vs. 30/38 (79) (p = 0.376)	NR	NR	NR	NR
Angel (41)	1/16 (6) vs. 2/24 (8) (p = NS)	NR	NR	NR	NR	NR
Belogolovkin (42)	2/36 (6) vs. 24/243 (10) (p = 0.40)	NR	NR	0/34 (0) vs 6/192 (3) (p = NS)	NR	NR
Haas (45)	11/77 (14) vs. 11/78 (14) (p = NS)	NR	NR	NR	NR	NR
Hwang (47)	NR	NR	NR	NR	NR	NR
Kim (39)[d]	10/153 (7) vs 22/157 (14) (OR 2.33 (1.06–5.10; p = 0.034))	NR	NR	NR	NR	NR
Kim (39)[e]	5/59 (8) vs. 22/157 (14) (p = NS)	NR	NR	NR	NR	NR

(*Continued*)

Table 4. (Continued).

Comparison/ study	GDM; *n* (%)	CD; *n* (%)	PPH; *n* (%)	Placental abruption; *n* (%)	HELLP; *n* (%)	Pulm. embolism; *n* (%)
Mostajeran (55)	NR	NR	NR	2/30 (7) vs. 2/30 (7) ($p > 0.05$)	NR	NR
Nevo (56)	5/64 (8) vs. 1/64 (2) (p = NS)	41/64 (64) vs. 40/64 (63) (p = NS)	NR	NR	NR	NR
Razaz (60)	13/45 (29) vs. 458/3340 (14) (p = NR)	31/45 (69) vs. 2341/3340 (70) (p = NR)	NR	NR	NR	NR
Selam (61)	NR	51/77 (66) vs. 73/140 (52) ($p < 0.05$)	1/77 (1) vs. 4/140 (3) (p = NS)	3/77 (4) vs. 2/140 (1) (p = NS)	NR	NR
Seo (62)	3/43 (7) vs. 4/264 (2) ($p = 0.022$)	NR	NR	NR	NR	NR
Silver (63)[f]	1/18 (6) vs. 2/54 (4) (p = NR)	6/18 (33) vs. 20/54 (37) (p = NR)	NR	2/18 (11) vs. 2/54 (4) (p = NR)	NR	NR
Silver (63)[g]	1/18 (6) vs. 1/54 (2) (p = NR)	6/18 (33) vs. 23/54 (43) ($p = 0.54$)	NR	2/18 (11) vs. 2/54 (4) (p = NR)	NR	NR
Singh (64)	NR	55/64 (86) vs. 89/100 (89) ($p = 0.568$)	NR	NR	NR	NR
Smith-Levitin (66)	3/59 (5) vs. 8/88 (9) (p = NS)	NR	NR	NR	NR	NR
Wang (67)	4/130 (3) vs. 3/140 (2) ($p = 0.417$)	NR	NR	NR	NR	NR
Yuce (68)[h]	NR	43/49 (88) vs. 96/117 (82) ($p = 0.403$)	NR	NR	0/49 (0) vs. 3/117 (3) ($p = 0.258$)	NR
Yuce (68)[i]	NR	43/49 (88) vs. 159/165 (97) ($p = 0.150$)	NR	NR	0/49 (0) vs. 0/165 (0)	NR

aOR, adjusted odds ratio; CD, cesarean delivery; GDM, gestational diabetes; HELLP, hemolysis, elevated liver enzymes, low platelets; PPH, postpartum hemorrhage; MFPR, multifetal pregnancy reduction; n, number; NR, not reported; NS, not significant; pulm., pulmonary; vs., versus.

[a]Defined as transfusion; [b]DCTA reduction to twin versus DCTA-expectant management; [c]TCTA reduction to twin versus TCTA-expectant management; [d]Early transvaginal embryo reduction (ER) versus ongoing twin pregnancy; [e]Late transvaginal fetal reduction (FR) versus ongoing twin pregnancy; [f]MFPR ≥3→2 vs. spontaneously conceived twins; [g]MFPR ≥3→2 vs. twins conceived through infertility therapy; [h]MFPR ≥3→2 vs. spontaneously conceived; [i]MFPR ≥3→2 vs. IVF conceived twins.

Two previously published systematic reviews are also reported on HDP after MFPR. In line with the results of our study, Zipori et al. (22) found no significant differences in their meta-analysis of HDP in women after reduced triplet pregnancies compared to non-reduced twin pregnancies (OR 1.23, 95% CI, 0.82–1.84; $p = 0.33$; $I^2 = 16\%$). However, in contrast to our meta-analysis, a control group of ongoing triplet pregnancies was not included. Raffé-Devine et al. (70) reported on maternal, fetal, and neonatal outcomes after MFPR from twin to singleton, triplet to twin or singleton and quadruplets to twins with different types of control groups without strict exclusion criteria (for example, no exclusion of selective reduction and MFPR from triplet to singleton). No significant trends with respect to HDP were reported, but no meta-analysis was performed.

The lower risk of HDP in women with twins after MFPR from a triplet or higher-order multifetal pregnancy compared to women with ongoing triplet pregnancies found in our study is in line with the latest evidence on the pathophysiology of HDP. The higher risk of HDP in women with multifetal compared to singleton pregnancies might be explained by a greater placental mass in which angiogenetic factors derived from abnormal placental tissue cause more severe endothelial dysfunction in the maternal cardiovascular system (71–73). By performing MFPR and reducing the number of fetuses in women with triplets and higher-order multifetal pregnancies, the enlargement of the harmful placental tissue may also reduce, possibly resulting in less endothelial dysfunction and lower risk of HDP. On the other hand, we found that women with twins after MFPR from all higher-order multifetal pregnancies have a significantly higher risk of developing GH compared to women with ongoing twins (Figure S6). We expect that this increased risk might be caused by a difference in the preexistent maternal cardiovascular health state of these women, with a higher maternal age at conception and more need for fertility treatments. Further research is still needed to explain the exact pathophysiology of HDP in women with multifetal pregnancies.

The results of this systematic review should be viewed in light of the following limitations. Only a small number of studies had a prospective design, so the conclusions of this review are based exclusively on retrospective data with its inherent shortcomings in terms of selection bias. For example, most individual studies included in this meta-analysis did not adjust appropriately for possible confounders of HDP such as maternal age, smoking status, obesity, or other preexisting diseases increasing risks for HDP. Furthermore, it is important to take into account that all included women in the MFPR groups were more likely to have used OI or ART (Table 3), possibly overestimating the incidence of HDP in individual studies. Nevertheless, when adjustment for these fertility treatments would take place, then the lower risk for HDP in women after MFPR from triplet or higher-order to twin pregnancy compared to women with ongoing triplets would only become more clear. Following the insufficient adjustment of possible confounders, in most studies a moderate risk of bias was found. A second cause of the moderate risk of bias found in most studies was the lack of documentation on the presence of preexisting hypertension of the included women, and, if data on preexisting hypertension were documented, women with such a history were not excluded from data analysis. Furthermore, the robustness of the results presented in this review is limited, as inaccurate or unprovided definition of HDP, GH, and PE might have biased our reported outcomes.

Remarkably, while MFPR decreased the occurrence of HDP in our two main comparisons, in the subgroup analyses, this result is driven by GH in one group (i.e., for MFPR triplet to twin versus ongoing triplet) and by PE in the other group (i.e., for MFPR higher-order to twin versus ongoing triplet). A post-hoc analysis showed that the main analyses (i.e., HDP as an outcome) were sufficiently powered, while the subgroup analyses for GH and PE were underpowered. For example, comparing the occurrence of PE in MFPR triplet to twin versus ongoing triplets in 555 versus 583 women achieved 73% power at a significance level of 0.05. In this specific comparison, to achieve a power of 80% each group would have to include 676 women. Therefore, the results of all these subgroup analyses should be interpreted with caution. Based on our results, when comparing MFPR triplet to twin versus ongoing triplets, 12 women should undergo MFPR to prevent one event of HDP.

In conclusion, this meta-analysis suggests that MFPR in women with triplet and higher-order multifetal pregnancies decreases the risk of HDP compared to women with ongoing triplet pregnancies. For MFPR from triplet to twin versus ongoing triplets this is driven by GH and for MFPR from higher-order to twin versus ongoing triplets this is driven by PE. These data can be used in the decision-making process of MFPR, in which the individual risk factors of HDP can be taken into account. To gain more insight into the effect of MFPR on HDP and to counsel women with multifetal pregnancies appropriately, future

studies should investigate meaningful parameters such as gestational age at onset, need for antihypertensive drug treatment and severity of manifestation of the disorder, with accurate use of diagnosis of HDP according to the most recent ISSHP classification (30).

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Author contributions

PB, CG, and MB conceived and designed the study. PB and LS performed the literature search. PB, JW, and EH screened articles for inclusion. PB and MB extracted data and appraised the risk of bias of the identified articles. PB and MB analyzed the data. PB, JW, LM, EP, CG, and MB interpreted the results and revised and contributed to the intellectual content of the manuscript. All authors approved the final version of the manuscript.

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