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Systematic review

Obstetric outcomes of twin pregnancies presenting with a complete hydatidiform mole and coexistent normal fetus: a systematic review and meta-analysis

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Background Epidemiological data on obstetric and oncologic complications in twin pregnancies combining a complete hydatidiform mole (CHM) coexisting with a normal fetus and placenta are limited.

Objectives To evaluate perinatal and obstetric outcomes for mother and fetus and risk of gestational trophoblastic neoplasia (GTN) in twin pregnancies including a CHM.

Search strategy PubMed, MEDLINE and EMBASE and the grey literature were searched for articles published between May 1980 and May 2019 using a protocol designed a priori and registered on PROSPERO (CRD42018112524).

Selection criteria Observational cohort studies of four or more cases confirmed by histopathology and providing data on pregnancy outcomes and GTN.

Data collection and analysis Two reviewers independently reviewed abstracts and full-text articles. The quality of the studies was assessed with the Newcastle-Ottawa scale and a meta-analysis was performed.

Main results Of the 344 abstracts identified, 14 studies (244 cases) met the eligibility criteria. The incidence of maternal complication in ongoing pregnancies was 80.8% and included vaginal bleeding, hyperthyroidism and pre-eclampsia. There were overall 91 (50%) live births in ongoing pregnancies and 83 (34%) of the total cases were subsequently diagnosed with GTN. Substantial and significant ($P < 0.001$) heterogeneity was found for the incidence of preeclampsia indicating variability in reporting the incidence of some obstetric complications between studies.

Conclusions Patients diagnosed with a twin pregnancy combining a CHM and an apparently normal fetus have a high risk of perinatal complications, low live-birth rates and around a third of them will develop a GTN and should be managed by specialised multidisciplinary teams.

Keywords Complete hydatidiform mole, gestational trophoblastic neoplasia, systematic review, twins.

Tweetable abstract Our study indicates a high rate of obstetric and oncologic complications in patients presenting with a complete hydatidiform mole and coexistent normal fetus.

Linked article This article is commented on by A Bhide, p. 1458 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16325

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Introduction

A twin pregnancy combining a complete or partial hydatidiform mole (CHM or PHM) and an apparently normal fetus is a rare obstetric condition which was first described in Laker in 1914.[1] The estimated prevalence of this condition varies widely between one in 22 000 and one in 100 000 pregnancies[2-5] and may be influenced by the accuracy of the clinical diagnosis and local epidemiological factors such as the incidence of multiple pregnancy in the corresponding population. Following uterine evacuation about 20% of patients with a CHM develop a gestational trophoblastic neoplasia (GTN) and 2% may also develop a choriocarcinoma.[6-9] The risk for a PHM to develop into a GTN is much lower and a PHM has rarely been reported in a multiple pregnancy.[2-9]

The most common presenting clinical symptoms of CHM is vaginal bleeding and most cases of single CHM and CHM coexisting with a normal fetus are more often diagnosed at the end of the first trimester of pregnancy.[10,11] Classically, women with ongoing second-trimester CHM also presented with uterine enlargement greater than expected for gestational age, abnormally high levels of serum human chorionic gonadotrophin (hCG) and complications including pre-eclampsia, hyperthyroidism, hyperemesis, anaemia and the development of ovarian theca-lutein cysts.[2-4] With the increased access to ultrasound imaging in early pregnancy, single CHM are now diagnosed and often evacuated before the onset of these symptoms.[9,12]

With the development of assisted reproductive techniques (ART) in the late 1970s, multiple pregnancy rates have increased markedly around the world and twin pregnancies now account for around 3% of all live births.[13,14] Both spontaneous twin pregnancies and those resulting from ART are associated with a higher risk of perinatal morbidity and mortality compared to singletons including preterm delivery, pre-eclampsia, gestational diabetes and intrauterine fetal growth restriction.[15-16] In addition, pregnant women presenting with a twin pregnancy where one gestational sac is a CHM are also at risk of GTN and thus their management presents unique clinical challenges.

The objective of this study was systematically to review the literature to determine the incidence of perinatal and obstetrics complications and risks of GTN in twin pregnancies with a CHM coexisting with an apparently normal fetus. We performed a meta-analysis to evaluate the heterogeneity in the distribution of these complications between studies. This review should inform clinical practice to aid counselling patients presenting with this complex condition.

Methods

Search strategies

The study was developed and completed in compliance with the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[17] and was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42018112524; www.crd.york.ac.uk/PROSPERO); PubMed, OVID MEDLINE and OVID EMBASE databases were searched for complying articles. Abstracts from these databases and from the grey (unpublished data) literature were searched for cohort studies and case series including four or more twin pregnancies combining a CHM and a normal fetus published between October 1980 and May 2019. The overall search strategy was inclusive of MeSH (Medical Subject Headings) headings for 'complete hydatidiform mole', 'twin pregnancy', 'twin gestation', 'molar placenta' AND 'obstetric complications' OR 'perinatal outcome', 'live-birth rate' OR 'preterm delivery', gestational trophoblastic neoplasia' OR 'gestational trophoblastic disease'. We excluded studies published before 1980, duplications of previously published data from the same centres or with indication of overlapping in the methodology, letters, editorials and case reports of up to three patients. The search was limited to human studies and articles published in English.

Selection of studies

Title and abstracts were independently assessed by two authors (N.Z.S. and Y.M). Additional relevant studies were identified from reference lists of reviews and editorials and by hand-searching key journals and websites based on our predefined inclusion. Two authors (N.Z.S and E.J.) carefully read the full texts independently for content, data extraction and analysis. All search results were combined in a reference database. Duplicates were removed by hand. Disagreements between the two original reviewers were resolved by discussion with the third investigator (R.M.). Study characteristics and outcomes were extracted using a predesigned data extraction protocol including: author institution, year of publication, country, dates and total number of cases, study type, maternal age, parity and gestational age at diagnosis. The primary outcome measures were perinatal and obstetric complications including the numbers of pregnancies complicated by vaginal bleeding, pre-eclampsia, hyperthyroidism, preterm birth or stillbirth. Secondary outcomes were the numbers of women who developed GTN.

Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies.[18] The NOS judges each study by three categories: selection of study group, comparability of the groups and the ascertainment of the outcome of interest. Each item was scored 'low', 'medium' or 'high' risk for bias. Studies that scored four stars for selection, two stars for comparability and three stars for ascertainment of the outcome were considered to have a low risk of bias. Studies with two or three stars for selection, one for comparability and two for outcome ascertainment were considered to have a medium risk of bias. We deemed any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains, to have a high risk of bias. No study was excluded based on the risk for bias. The scoring of each study was blindly conducted by at least two authors independently and then discussed in the event of inconsistency.

Data analysis

Meta-analysis was performed for pooling results from various selected studies and to evaluate the variation in study outcomes between studies using the 'metaprop' (StataCorp) routine. We used a random effects model and exact confidence intervals for proportion in pooling the results to adjust for variations among studies. Statistical heterogeneity was assessed with the I^2 statistic (the proportion of variation in study estimates because of heterogeneity rather than sampling error). The rate of each outcome was estimated over all studies that provided the necessary data. Forest plots are presented to summarise graphically the study results and the pooled results. Pooled proportions were presented with a 95% confidence interval and the I^2 using STATA 14.3 (STATA, College Station, TX, USA).

Patient and public involvement

Our study was a literature review and did not include patients as study participants. Patients were not involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study or dissemination of results.

Results

Study selection and description

The search identified 344 citations; of these, 14 articles were included in the final analysis. The process of selection of papers is summarised in Figure S1. All studies were retrospective and only four of the studies were published before the year 2000 (Table S1). Of the included studies, eight were from a single medical centre, three from a regional specialist oncology unit, two involved one or more centres and one was from a national specialist oncology unit. There were 12 case series and two cohort studies including data from eight different countries.

Quality assessment

Eleven of the 14 studies included in the final review had a low risk of bias for sample selection, 11 had a low risk of bias for outcome assessment and nine had a low risk of bias for comparability of cohorts (Figure S2). Overall, seven studies had a low risk of bias.

Synthesis of results

A total of 244 cases of CHM with a coexisting fetus confirmed at birth by histopathology were included in the analysis. The mean/median maternal age ranged between 24 and 32 years of age and the mean/median gestation age at diagnosis between 12 and 23 weeks, with the most recent studies diagnosed between 12 and 17 weeks (Table S1).

Sixty-two pregnancies (25.4%) were electively terminated before 24 weeks of gestation (Table 1). The overall incidence of antenatal maternal complications in the 182 ongoing pregnancies was 80.8% (n = 147), including 26 (14.3%) pregnancies complicated by pre-eclampsia. One cohort study did not report on vaginal bleeding or hyperthyroidism.[23] In the remaining studies, which included a total of 129 pregnancies, 91 (70.5%) were complicated by vaginal bleeding and 30 (23.3%) by hyperthyroidism. Overall there were 91 (50%) live births in ongoing pregnancies, 71 (78%) of which were born before term. Intrauterine fetal death (IUFD) was reported in 73 (40.1%) of the ongoing pregnancies.

Of the 244 cases included in the review, 83 (34%) were subsequently diagnosed with GTN. There was no report of maternal death.

The levels of overall heterogeneity between study estimates for the incidence of maternal antenatal complications, pre-eclampsia and live-birth rates in the 182 ongoing pregnancies and the incidence of GTN in all 244 pregnancies are displayed in Figures 1–4. Moderate heterogeneity was found for the incidence of maternal antenatal complications (I^2 = 32.03%) and GTN rate (I^2 = 35.27%). Substantial and significant ($P < 0.001$) heterogeneity (I^2 = 61.58%) was found for the analysis of the incidence of pre-eclampsia.

Discussion

Main findings

Our results indicate that ongoing twin pregnancies combining a CHM and a normal fetus and placenta are associated with a high rate of perinatal morbidity including IUFD, pre-eclampsia and term delivery. Patients with this condition are also at very high risk of subsequently developing GTN, independently of the gestation age at which the pregnancy was terminated or delivered. Our findings emphasise the need for ongoing twin pregnancies including a CHM to be cared for by a multidisciplinary team in a centre with access to neonatal intensive care for very premature newborns and to be offered post-pregnancy follow up in a centre specialising in the management of GTN.

Strengths

This is the first review and meta-analysis examining the outcomes of twin pregnancies combining a CHM and a normal fetus. We performed a broad search for cases series of four or more cases and cohort studies with histopathological confirmation of molar tissue at delivery in an attempt to overcome the rarity of the cases and reduce the risk of bias selection associated with single case report. We started our search in 1980, corresponding to

Table 1. Number of cases and outcome data of the included studies

Author et al. (Year)	Number of cases	Elective TOP *n*	Vaginal Bleeding *n*	Hyperthyroidism *n*	Pre-eclampsia *n*	IUFD *n*	Live birth *n*	GTN *n*
Block et al. (1982)[19]	6	0	3	0	5	2	2	1
Steller et al. (1994)[20]	8	5	7	0	2	0	1	5
Ishii et al. (1998)[21]	6	3	4	0	0	2	2	3
Fishman et al. (1998)[22]	7	0	0	0	0	0	2	4
Sebire et al. (2002)[23]	77	24	N/A	N/A	3	31	20	15
Marcorelles et al. (2005)[24]	4	1	3	0	1	1	2	1
Wee et al. (2005)[4]	8	1	8	0	1	2	7	3
Neimann et al. (2007)[25]	8	5	7	0	0	2	7	2
Massardier et al. (2009)[26]	14	3	3	4	4	3	3	7
Lee et al. (2010)[27]	6	1	2	4	2	2	1	3
Kutuk et al. (2014)[28]	7	2	2	0	0	4	1	1
Giorgione et al. (2017)[29]	13	2	8	2	0	5	5	4
Lin et al. (2017)[30]	70	10	36	20	7	17	36	31
Wang et al. (2018)[31]	10	5	8	0	1	2	2	3
Total	244	62	91	30	26	73	91	83

GA, gestational age; GTN, gestational neoplasia; IUFD, intrauterine fetal death; N/A, not available; PIH, pregnancy-induced hypertension; TOP, termination of pregnancy.

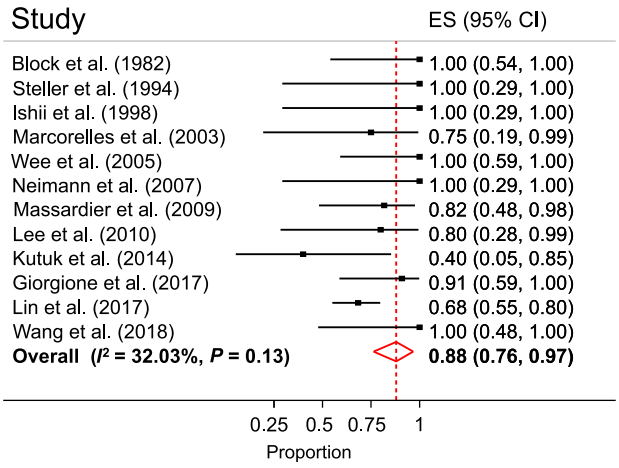

Figure 1. Forest plots showing the heterogeneity of incidence data for maternal complications. Only first author's name is given for each reference. ES = effect size; CI = confidence interval.

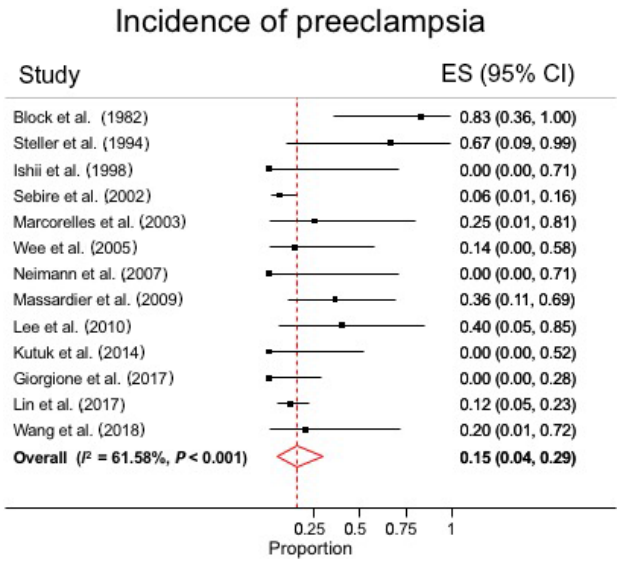

Figure 2. Forest plots showing heterogeneity of incidence data for pre-eclampsia. Only first author's name is given for each reference. ES = effect size; CI = confidence interval.

the time of the first detailed antenatal ultrasound description of a case by Sauerbrei et al.,[32] to increase the probability of an accurate diagnosis and reporting of the condition. To decrease the heterogeneity of the included variables in the final analysis, we only included the data from ongoing pregnancies and from cohort series of four or more cases.

Limitations

The main limitation of this study is its retrospective nature, the lack of population data and variation in diagnosis and managing protocols between centres in different countries. We were therefore not able to evaluate the overall incidence and possible changes in the incidence of the

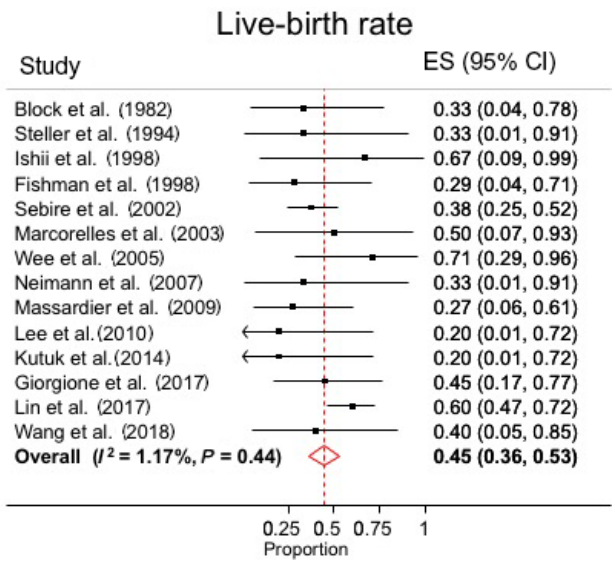

Figure 3. Forest plots showing heterogeneity of incidence data for live-birth rates. Only first author's name is given for each reference. ES = effect size; CI = confidence interval.

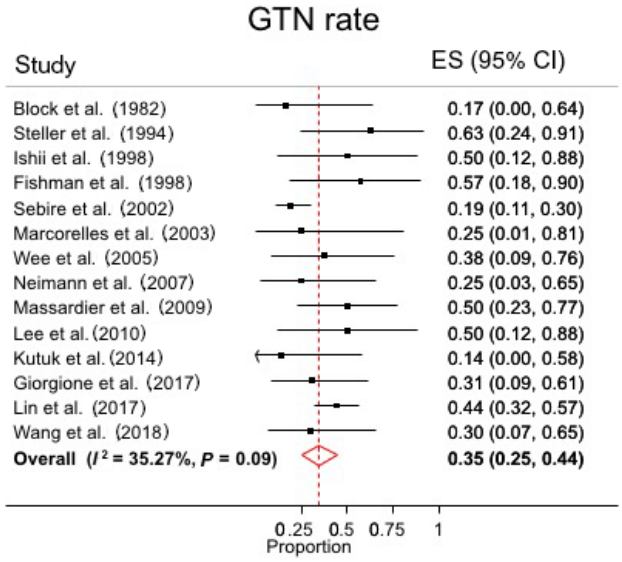

Figure 4. Forest plots showing heterogeneity of incidence data for gestational trophoblastic neoplasia (GTN). Only first author's name is given for each reference. ES = effect size; CI = confidence interval.

condition between 1980 and 2019 but they have probably increased during that period due to the increase in number of multiple pregnancies resulting from ART.[13,14] Our findings must also be interpreted in the context of individual study design. One large cohort study from a centre specialising in the post-pregnancy follow up and management of GTN did not report on vaginal bleeding and hyperthyroidism. These complications are commonly associated with the development of a CHM[6,7] and a substantial significant heterogeneity in the rate of pre-eclampsia (Figure 2) suggests that the rate of some of the different maternal complications may have been underevaluated. This may be especially true when outcome data are obtained using questionnaires from clinicians who may not have been directly involved in the individual patients' care, and analysed retrospectively.

Interpretation

Vaginal bleeding is the most common clinical complication of singleton CHM and is due to the superficial placentation and the premature entry of maternal blood in the intervillous space.[33,34] Chronic heavy vaginal bleeding can lead to severe maternal anaemia and is more commonly observed in cases where the CHM or the normal placenta is praevia.[35-37] Vaginal bleeding causes focal inflammation and is also a well-known risk factor for premature rupture of the membranes and premature delivery.[38,39] Over 70% of the patients included in the present study were found to have different degrees of vaginal bleeding. This complication certainly contributes to the high rate of premature birth in twin pregnancies including a CHM.

Early onset pre-eclampsia and eclampsia were well-known complications of single CHM before the advent of prenatal ultrasound diagnosis.[9,12] Women with twin pregnancies have higher rates of pre-eclampsia compared with those with singleton.[40] Similarly to singleton pregnancies, the risks of pre-eclampsia in twins are higher in nulliparous and older mothers.[41] A recent Norwegian population-based register study has found an incidence of pre-eclampsia of 3.4% in singletons compared with 11.8% in twins.[42] Of the 182 ongoing pregnancies included in the present review, 26 (14.3%) were diagnosed with pre-eclampsia. Three of the cases included in our analysis were from a large cohort study[23] with limited data on maternal characteristics and complications (Table 1). Without the data from this study, the rate of pre-eclampsia was 21.9% (23/105), suggesting that twin pregnancies including a CHM are at higher risks of pre-eclampsia than are normal twin pregnancies.

Independent of zygosity, twin pregnancies are also associated with higher risks preterm delivery[43,44] and around 45% of twins are born preterm.[43] The prospective risk of IUFD at ≥34 weeks' gestation is 0.17% for dichorionic twins.[44,45] There is no significant difference in the risk of stillbirth between dichorionic and monochorionic twins.[43,45] Our analysis indicates that twin pregnancies combining a CHM and a normal fetus both have a very high rate of preterm delivery and IUFD, with only a 50% overall live-birth rate. Pre-eclampsia and chronic vaginal bleeding are probably both major contributors to these perinatal complications.

Clinical hyperthyroidism and ovarian thecal cysts have been reported in around 2 and 9% of single CHM, respectively.[6,9] These complications are the side-effect of increased hCG synthesis by the hyperplasic trophoblast of molar tissue. In the present review, hyperthyroidism was reported in 23.3% of the cases and was found in association with a very high level of maternal serum hCG in all nine corresponding studies[4,19,20,24,25,27,28,30,31]. These levels can reach 200 multiples of the normal median for gestational age[46] and maternal serum hCG can be useful in the differential ultrasound diagnosis between hydatidiform and pseudo-hydatidiform moles associated with a normal fetus and in the antenatal management of twin pregnancies combining a CHM and a normal fetus and placenta.[4,10] Ovarian thecal cysts were only reported in one cases series[4] and thus the incidence of this complication could not be evaluated by the present review.

GTN has been reported in around 20% of the cases after evacuation of a single CHM[6,7,9] and the risk of post-molar GTN is not affect by the gestational age at diagnosis or evacuation.[9] Data on post-molar GTN were available for all 244 cases included in the present review and our meta-analysis indicated a low level of overall heterogeneity between study estimates. We found that 34% of the cases were subsequently diagnosed with GTN but we could not evaluate the effect of early elective pregnancy termination on the risk of post-molar GTN. However, our data indicate that the incidence of post-molar GTN is higher in twin pregnancies combining a CHM and a normal fetus than in single CHM.

Conclusion

The findings of our review and meta-analysis will help clinicians counsel patients presenting with a twin pregnancy combining a CHM and a normal fetus. Due to the worldwide increase in the use of ART, the incidence of this complex obstetric complication is likely to increase in the future. Pre-eclampsia, IUFD and preterm delivery were the commonest perinatal and obstetric complications and their incidence was higher than the incidence reported in the international literature for normal twin pregnancies. The high rate of adverse perinatal outcomes highlights the need for these patients to be followed up and delivered in centres with expertise in managing high-risk pregnancies and with access to intensive neonatal care for very premature newborns. Patients should also be informed of the high risk of GTN, independently of gestational age when the pregnancy ended, and thus of the need for long-term follow up by a specialist oncology team.

Disclosure of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

NZS extracted the data, performed the analysis and data interpretation, and drafted the manuscript. YM assisted with data extraction and analysis. RM contributed to data, extraction, analysis and data interpretation of the findings. EJ conceived of and designed the study, contributed to the data analysis and interpretation of the findings. EJ is the guarantor for the study. All authors contributed to the final manuscript.

Details of ethics approval

Not applicable.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. PRISMA flow diagram of study selection.

Figure S2. Quality assessment.

Table S1. Characteristics of included studies. ■

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