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Perinatal mortality, timing of delivery and prenatal management of monoamniotic twin pregnancy: systematic review and meta-analysis

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KEYWORDS: monoamniotic twin pregnancy; neonatal outcome; systematic review; timing of delivery

ABSTRACT

Objective *To quantify the rate of perinatal mortality in monochorionic monoamniotic (MCMA) twin pregnancies, according to gestational age, and to ascertain the incidence of mortality in pregnancies managed as inpatients compared with those managed as outpatients.*

Methods *MEDLINE, EMBASE and CINAHL databases were searched for studies on monoamniotic twin pregnancy. The primary outcomes explored were the incidence of intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in MCMA twins at different gestational-age windows (24–30, 31–32, 33–34, 35–36 and ≥ 37 weeks of gestation). The secondary outcomes were the incidence of IUD, NND and PND in MCMA twins according to the type of fetal monitoring (inpatient* vs *outpatient), and the incidence of delivery ahead of schedule. Random-effects model meta-analyses were used to analyze the data.*

Results *Twenty-five studies (1628 non-anomalous twins reaching 24 weeks of gestation) were included. Single and double intrauterine deaths occurred in 2.5% (95% CI, 1.8–3.3%) and 3.8% (95% CI, 2.5–5.3%) of cases, respectively. IUD occurred in 4.3% (95% CI, 2.8–6.2%) of twins at 24–30 weeks, in 1.0% (95% CI, 0.6–1.7%) at 31–32 weeks and in 2.2% (95% CI, 0.9–3.9%) at 33–34 weeks of gestation, while there was no case of IUD, either single or double, from 35 weeks of gestation. In MCMA twin pregnancies managed mainly as inpatients, the incidence of IUD was 3.0% (95% CI, 1.4–5.2%), while the corresponding figure for those managed mainly as outpatients was 7.4% (95% CI, 4.4–11.1%). Finally, 37.8% (95% CI, 28.0–48.2%) of MCMA pregnancies were delivered before the scheduled time, due mainly to spontaneous preterm labor or abnormal cardiotocographic findings.*

Conclusions *MCMA twins are at high risk of perinatal loss during the third trimester of pregnancy, with the large majority of such losses occurring as apparently unexpected events. Inpatient management seems to be associated with a lower rate of mortality, although further studies are needed in order to establish the appropriate type and timing of prenatal assessment in these pregnancies. Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.*

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INTRODUCTION

Chorionicity is the main determinant of perinatal outcome in twin pregnancy. Monochorionic (MC) twin pregnancies are at higher risk of perinatal mortality and morbidity compared with dichorionic (DC) pregnancies due to the excess risk of preterm birth, growth discordance and complications unique to MC placentas, such as twin–twin transfusion syndrome (TTTS), twin reversed arterial perfusion (TRAP) sequence and selective intrauterine growth restriction[1–7]. Prenatal identification of monochorionic monoamniotic (MCMA) twins is fundamental because monoamnionicity carries a further increased risk of adverse pregnancy outcome compared with MC diamniotic pregnancies, thus ideally requiring a tailored approach[8].

Despite this, the optimal type of management of MCMA pregnancy has still to be elucidated. There is no randomized controlled trial addressing the type and frequency of follow-up in MCMA pregnancy, and no specific recommendation on how to manage MCMA twins has been provided by the different national bodies. MCMA pregnancies are usually delivered between 32 and 34 weeks of gestation in view of the reported high risk of unexpected fetal loss with advancing gestation[9]. The antenatal management protocol of monoamniotic twins is also controversial, with some studies advocating inpatient follow-up of these pregnancies with serial ultrasound and cardiotocographic (CTG) assessment, while others report no difference in the perinatal outcome between cases managed as inpatients and those managed as outpatients[9]. However, published studies are likely to be biased by their retrospective design, small sample size and inclusion of cases with fetal anomalies, thus making it difficult to extrapolate robust evidence of the actual risk of perinatal mortality in these pregnancies.

The primary aim of this systematic review was to quantify the incidence of perinatal mortality in MCMA twin pregnancies, according to gestational age. The secondary aim was to ascertain the risk of mortality in pregnancies managed as inpatients compared with those managed as outpatients.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to an *a-priori*-designed protocol recommended for systematic reviews and meta-analyses[10]. MEDLINE, EMBASE and CINAHL were searched electronically on 17 December 2017 and updated on 17 July 2018, utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'monoamniotic', 'twin pregnancies' and 'outcome' (Table S1). The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were hand-searched for additional reports. PRISMA and MOOSE guidelines were followed[11,12]. The study was registered with the PROSPERO database (registration number: CRD42016043062).

Study selection, data collection and data items

The primary outcome explored in the present systematic review was the incidence of intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in MCMA twins in the following gestational age windows: 24–30 weeks, 31–32 weeks, 33–34 weeks, 35–36 weeks and $\geq$ 37 weeks.

IUD was defined as fetal demise from 24 weeks of gestation and was divided into single (sIUD) and double (dIUD) according to the death of one or both twins, respectively. NND was defined as the death of at least one of the newborns up to 28 days postpartum, while PND was defined as IUD plus NND. We also aimed to categorize the cause of IUD into those related to the presence of TTTS or growth restriction and those that were sudden or unexpected, defined as IUD occurring in a MCMA twin without a prior recognizable chronic condition such as transfusion events or growth abnormalities.

The secondary outcomes were the incidence of IUD, NND and PND in twins according to the type of fetal monitoring. For the purpose of this analysis, twin pregnancies were divided into those admitted electively to the hospital for fetal monitoring (inpatients) and those followed up as outpatients. Finally, we explored the incidence of delivery ahead of schedule in MCMA twin pregnancies scheduled for elective delivery at 32 weeks and those scheduled for delivery between 32 and 34 weeks of gestation.

Only studies reporting the number of MCMA twin pregnancies in each gestational-age window and the relative number of deaths were considered suitable for inclusion. Studies including cases with fetal anomaly were excluded in view of the higher risk of mortality in twins affected by structural or chromosomal anomaly. Only full-text articles were considered eligible for inclusion. Case reports, conference abstracts and case series with fewer than three cases were excluded to avoid publication bias. Furthermore, studies published before 2000 were not included, as advances in management of twin pregnancies make them less relevant.

Two authors (F.D., D.B.) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus; full-text copies of those papers were obtained and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus was reached between them or by discussion with a third author. If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such to suggest

that this information would have been recorded initially, the authors were contacted.

Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS) for case–control studies. According to NOS, each study is judged on three broad perspectives: selection of the study groups, comparability of the groups and ascertainment of the outcome of interest[13]. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of study. Assessment of the comparability of the study includes evaluation of the comparability of cohorts based on the design or analysis. Finally, ascertainment of the outcome of interest includes evaluation of the type of assessment of the outcome of interest, length and adequacy of follow-up. According to NOS, a study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability[13].

Statistical analysis

The prevalence of each of the explored outcomes was evaluated in MCMA twins, overall and according to gestational age; the overall number of fetuses was used as the denominator for each proportion. Proportion meta-analysis using a random-effects model to account for interstudy heterogeneity was used to analyze the data. Potential publication bias was assessed either graphically, displaying the odds ratios of individual studies *vs* the logarithm of their standard errors (funnel plots), or formally, using Egger's regression asymmetry test[14]. Tests for publication bias were not performed when the overall number of included studies was less than 10, in view of their low power[15]. All analyses were carried out using STATA, version 13.1 (Stata Corp., College Station, TX, USA).

RESULTS

General characteristics

A total of 607 articles were identified and assessed with respect to their eligibility for inclusion. Of those, 53 had the full text assessed for eligibility and 25 were included in the systematic review (Table 1, Figure 1)[16–40]. Table S2 lists the excluded studies and the reason for exclusion. The 25 studies included 1068 MCMA pregnancies (2136 twins); information on perinatal mortality according to the gestational age at loss was provided for 814 non-anomalous twin pairs (1628 twins) reaching 24 weeks of gestation, which represent the population analyzed in this systematic review.

Table 1 General characteristics of included studies on outcome of monoamniotic twin pregnancy

Study	*Country*	*Study design*	*Study period*	*Antenatal management*	*GA at delivery (weeks)*	*Pregnancies (n)*
Saccone (2019)[16]	Italy, Spain, UK, USA	Retro	2010–2017	Inpatient or outpatient	32–34	185
Glinianaia (2019)[17]	UK	Retro	2000–2013	Inpatient or outpatient	32–35	55
Kristiansen (2015)[18]	Denmark	Retro	2008–2011	Outpatient	34	24
Prefumo (2015)[19]	Italy	Retro	2004–2013	Inpatient	32	20
Anselem (2015)[20]	France	Retro	1993–2014	Outpatient	36	38
Van Mieghem (2014)[21]	Canada, Belgium, The Netherlands, Austria, Switzerland, USA	Retro	2003–2012	Inpatient or outpatient	32–34	193
Aurioles-Garibay (2014)[22]	USA	Retro	2007–2013	Inpatient	32	6
Murata (2013)[23]	Japan	Retro	2001–2011	Inpatient	32–34	38
Suzuki (2013)[24]	Japan	Retro	NS	NS	Up to 39	18
Dias (2011)[25]	UK	Retro	1997–2008	Outpatient	34	30
Quinn (2011)[26]	USA	Retro	2000–2009	Inpatient	34	13
Assuncao (2010)[27]	Brazil	Retro	2003–2006	Inpatient or outpatient	34	38
Baxi (2010)[28]	USA	Retro	2001–2009	Inpatient	34	25
Hack (2009)[29]	The Netherlands	Retro	2000–2007	Inpatient or outpatient	32–34	98
Arabin (2009)[30]	The Netherlands	Retro	NS	Outpatient	NS	17
Heflin (2008)[31]	USA	Retro	NS	Outpatient	33–34	3
Cordero (2006)[32]	USA	Retro	1990–2005	Inpatient or outpatient	32–34	36
Pasquini (2006)[33]	UK	Retro	1994–2005	Outpatient	32	20
DeFalco (2006)[34]	USA	Retro	1991–2001	Inpatient or outpatient	NS	23
Heyborne (2005)[35]	USA	Retro	1993–2003	Inpatient or outpatient	32–34	96
Ezra (2005)[36]	Israel	Retro	1986–2002	Inpatient or outpatient	NS	33
Demaria (2004)[37]	France	Retro	1993–2001	Outpatient	36	19
Sau (2003)[38]	UK	Retro	1994–2000	Outpatient	32	7
Allen (2001)[39]	Canada	Retro	1993–2000	Inpatient or outpatient	32–35	25
Sebire (2000)[40]	UK	Retro	1992–1998	Inpatient or outpatient	34	8

Only first author is given for each study. GA, gestational age; NS, not stated; Retro, retrospective.

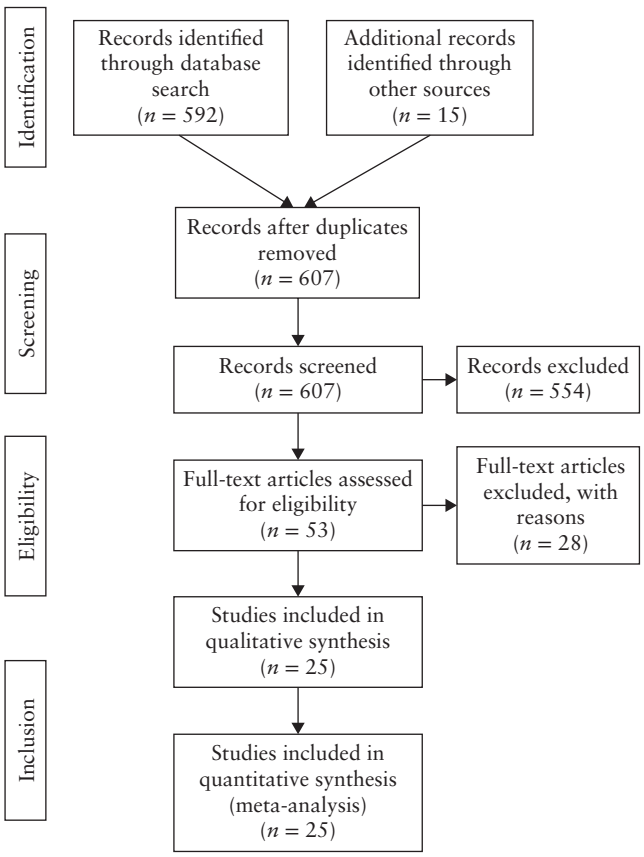

Figure 1 Flowchart of inclusion of studies on outcome of monoamniotic twin pregnancy.

Table 2 Quality assessment according to Newcastle–Ottawa Scale of included studies on outcome of monoamniotic twin pregnancy

Study	*Selection*	*Comparability*	*Outcome*
Saccone (2019)[16]	★★★	★★	★★
Glinianaia (2019)[17]	★★★	★★	★★
Kristiansen (2015)[18]	★★★	★	★★
Prefumo (2015)[19]	★★	★	★★
Anselem (2015)[20]	★★	★	★★
Van Mieghem (2014)[21]	★★★	★	★★
Aurioles-Garibay (2014)[22]	★★	★	★
Murata (2013)[23]	★★	★	★★
Suzuki (2013)[24]	★★	★	★
Dias (2011)[25]	★★	★	★
Quinn (2011)[26]	★★	★★	★★
Assuncao (2010)[27]	★★	★	★
Baxi (2010)[28]	★★	★	★★
Hack (2009)[29]	★★	★	★
Arabin (2009)[30]	★	★	★
Heflin (2008)[31]	★★	★	★★
Cordero (2006)[32]	★★	★	★★
Pasquini (2006)[33]	★★★	★	★★
DeFalco (2006)[34]	★★	★	★★
Heyborne (2005)[35]	★★★	★	★★
Ezra (2005)[36]	★★	★	★
Demaria (2004)[37]	★★	★	★★
Sau (2003)[38]	★★	★	★
Allen (2001)[39]	★★	★	★★
Sebire (2000)[40]	★	★	★

Only first author is given for each study. Study can be awarded maximum of one star for each numbered item within selection and outcome categories. Maximum of two stars can be given for comparability.

The results of quality assessment of the included studies using the NOS are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of the study groups, as well as for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size, different gestational ages at ultrasound examination and lack of information on prenatal management of twins affected by weight discordance.

Synthesis of results

Twenty-four studies including 814 non-anomalous MCMA pregnancies (1628 twins) reaching 24 weeks of gestation explored the incidence of mortality according to gestational age. Overall IUD, including either sIUD or dIUD, occurred in 5.8% (95% CI, 4.0–8.1%) of twins, while the corresponding figures for sIUD and dIUD were 2.5% (95% CI, 1.8–3.3%) and 3.8% (95% CI, 2.5–5.3%). The incidence of NND was 2.6% (95% CI, 1.9–3.4%) (Table 3, Figure 2).

The incidence of mortality varied according to gestational-age window. IUD occurred in 4.3% (95%

Table 3 Pooled proportions of overall, single (sIUD) and double (dIUD) intrauterine death (IUD), and neonatal (NND) and perinatal (PND) death in monoamniotic twins, overall and according to gestational age

Outcome	*Studies* (n)	*Fetuses* (n/N)	*Pooled proportions (95% CI) (%)*	I^2 *(%)*
Overall mortality				
Overall IUD	24	106/1628	5.84 (4.0–8.1)	59.0
sIUD	24	38/1628	2.53 (1.8–3.3)	0
dIUD*	24	68/1628	3.77 (2.5–5.3)	44.2
NND	24	37/1628	2.56 (1.9–3.4)	0
PND	24	143/1628	7.91 (5.9–10.2)	51.7
24–30 weeks				
Overall IUD	24	84/1628	4.32 (2.8–6.2)	54.1
sIUD	24	30/1628	1.99 (1.4–2.7)	0
dIUD*	24	54/1628	2.87 (1.8–4.2)	41.8
NND	24	35/1628	2.45 (1.8–3.3)	0
PND	24	119/1628	6.21 (4.4–8.3)	51.1
31–32 weeks				
Overall IUD	24	11/1266	1.03 (0.6–1.7)	0
sIUD	24	5/1266	0.59 (0.2–1.1)	0
dIUD*	24	6/1266	0.71 (0.3–1.2)	0
NND	24	2/1266	0.59 (0.2–1.1)	0
PND	24	13/1266	1.30 (0.7–2.0)	0
33–34 weeks				
Overall IUD	18	11/606	2.16 (0.9–3.9)	28.4
sIUD	18	3/606	0.99 (0.4–1.9)	0
dIUD*	18	8/606	1.56 (0.6–3.0)	24.6
NND	18	0/606	0 (0–1.4)	0
PND	18	11/606	2.16 (0.9–3.9)	28.4
35–36 weeks				
Overall IUD	11	0/150	0 (0–4.0)	0
sIUD	11	0/150	0 (0–4.0)	0
dIUD*	11	0/150	0 (0–4.0)	0
NND	11	0/150	0 (0–4.0)	0
PND	11	0/150	0 (0–4.0)	0

*dIUD counted as double event.

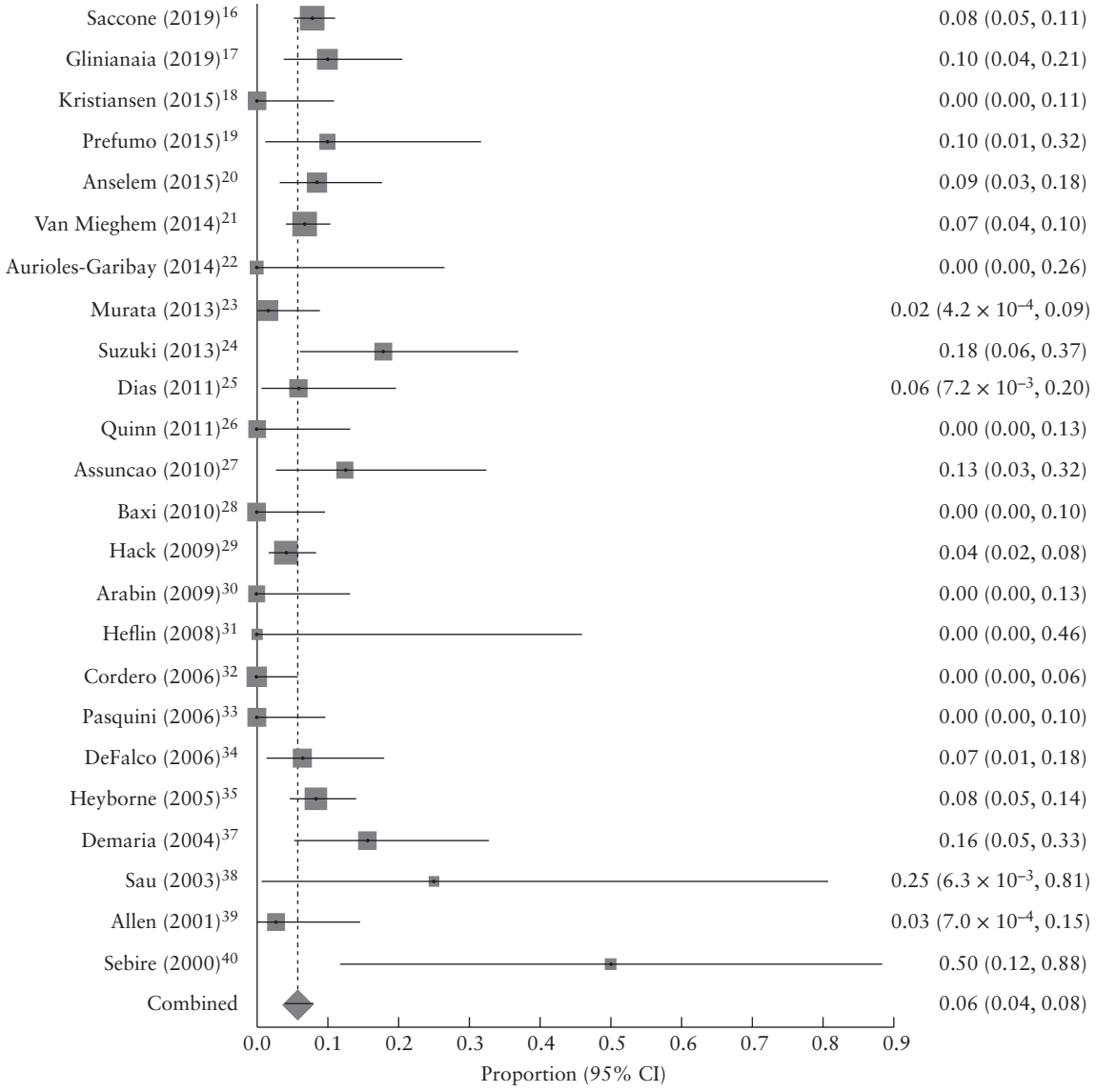

Figure 2 Pooled proportions (95% CI) of overall intrauterine death in monochorionic monoamniotic twin pregnancy.

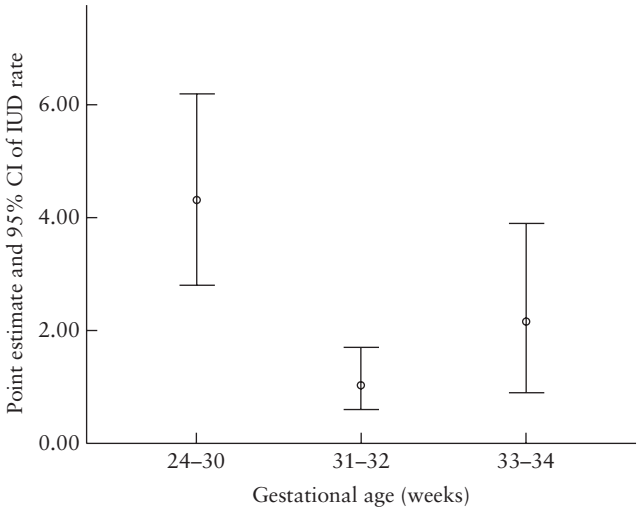

Figure 3 Point estimates (95% CI) of intrauterine death (IUD) rates in monochorionic monoamniotic twin pregnancy, according to gestational age.

CI, 2.8–6.2%) of cases at 24–30 weeks, 1.0% (95% CI, 0.6–1.7%) at 31–32 weeks and in 2.2% (95% CI, 0.9–3.9%) at 33–34 weeks of gestation, while there was no IUD, either single or double, from 35 weeks of gestation, although the sample size was small (Table 3, Figure 3).

sIUD and dIUD occurred, respectively, in 2.0% (95% CI, 1.4–2.7%) and 2.9% (95% CI, 1.8–4.2%) of twins at 24–30 weeks, 0.6% (95% CI, 0.2–1.1%) and 0.7% (95% CI, 0.3–1.2%) at 31–32 weeks, and 1.0% (95% CI, 0.4–1.9%) and 1.6% (95% CI, 0.6–3.0%) of cases at 33–34 weeks of gestation. Finally, NND occurred in 2.5% (95% CI, 1.8–3.3%) of cases at 24–30 weeks and 0.6% (95% CI, 0.2–1.1%) at 31–32 weeks, while there was no death later in gestation (Table 3).

When analyzing those studies reporting the etiology of IUD, 29.5% (95% CI, 13.5–48.8%; $I^2 = 55.2\%$) of the overall losses were due to TTTS or growth restriction, while 54.0% (95% CI, 37.1–71.3%; $I^2 = 42.8\%$) were unexpected IUD. Furthermore, from 31 weeks of

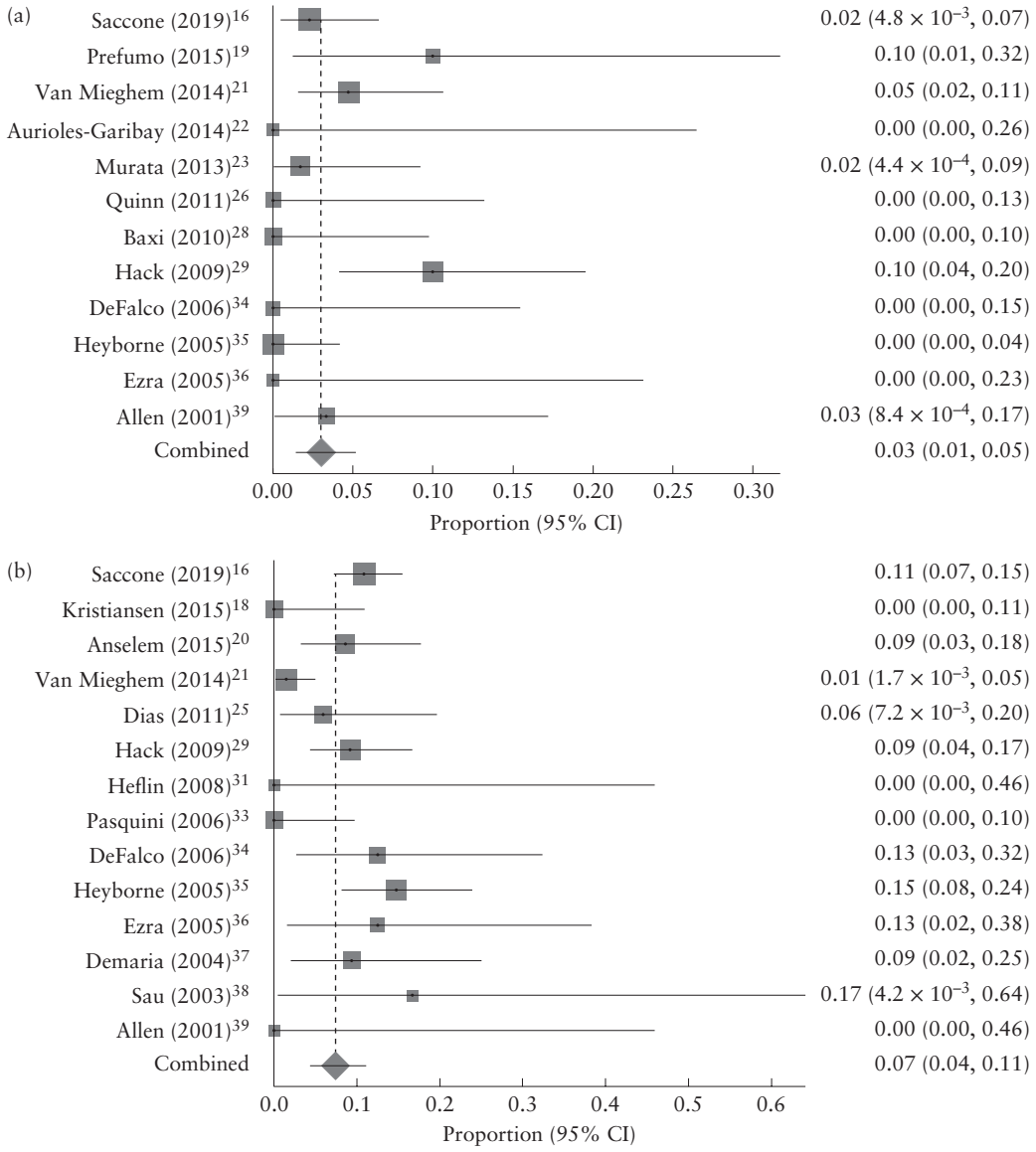

Figure 4 Pooled proportions (95% CI) of overall intrauterine death in monochorionic monoamniotic twin pregnancies managed mainly as inpatients (a) and those managed mainly as outpatients (b).

Table 4 Pooled proportions of overall, single (sIUD) and double (dIUD) intrauterine death (IUD), and neonatal (NND) and perinatal (PND) death in monoamniotic twins treated mainly as inpatients and those treated mainly as outpatients

Outcome	*Studies* (n)	*Fetuses* (n/N)	*Pooled proportions (95% CI) (%)*	I^2 *(%)*
Inpatient management				
Overall IUD	12	19/610	3.02 (1.4–5.2)	40.7
sIUD	12	9/610	1.85 (0.9–3.1)	0
dIUD*	12	10/610	1.61 (0.5–3.3)	39.8
NND	12	8/610	1.52 (0.7–2.6)	0
PND	12	27/610	3.72 (1.5–6.9)	63.5
Outpatient management				
Overall IUD	14	67/830	7.40 (4.4–11.1)	63.5
sIUD	14	17/830	2.38 (1.2–4.0)	29.6
dIUD*	14	50/830	5.33 (3.2–8.0)	46.9
NND	14	21/830	2.65 (1.6–3.9)	6.4
PND	14	88/830	9.53 (5.9–13.9)	67.0

*dIUD counted as double event.

gestation, all IUDs included in the present systematic review were reported to be unexpected and not the consequence of a chronic condition that can be potentially identified *in utero*.

Twenty studies reported the incidence of mortality in pregnancies managed mainly as inpatients and/or those followed up as outpatients. In MCMA twin pregnancies managed mainly as inpatients, the incidence of IUD was 3.0% (95% CI, 1.4–5.2%), while the corresponding figures for sIUD and dIUD were 1.9% (95% CI, 0.9–3.1%) and 1.6% (95% CI, 0.5–3.3%) (Figure 4, Table 4). Conversely, in MCMA twin pregnancies managed mainly as outpatients, IUD occurred in 7.4% (95% CI, 4.4–11.1%) of twins, while sIUD and dIUD occurred in 2.4% (95% CI, 1.2–4.0%) and 5.3% (95% CI, 3.2–8.0%), respectively.

In pregnancies managed mainly as inpatients, 27.9% (95% CI, 10.4–49.9%; $I^2 = 0\%$) of the IUDs were due

Table 5 Pooled proportions of delivery ahead of schedule in monoamniotic twin pregnancy

Outcome	*Studies* (n)	*Pregnancies* (n/N)	*Pooled proportions (95% CI) (%)*	I^2 *(%)*
All				
Overall	15	216/606	37.81 (28.0–48.2)	79.7
Delivery due to PTB	13	65/178	35.73 (29.0–51.6)	72.2
Delivery due to CTG anomaly	13	80/178	39.15 (23.6–55.9)	73.6
Delivery due to other reason	13	33/178	23.85 (12.0–38.52)	68.9
Delivery scheduled at 32 weeks				
Overall	5	6/39	18.46 (6.5–34.8)	24.8
Delivery due to PTB	4	1/6	22.05 (20.1–55.0)	0
Delivery due to CTG anomaly	4	1/6	22.64 (13.4–59.0)	15.8
Delivery due to other reason	4	4/6	64.37 (28.2–93.0)	12.3
Delivery scheduled at 32–34 weeks				
Overall	7	154/474	34.70 (26.6–43.2)	65.2
Delivery due to PTB	5	52/112	39.96 (21.0–60.6)	75.1
Delivery due to CTG anomaly	5	38/112	35.40 (17.2–56.1)	75.4
Delivery due to other reason	5	22/112	22.90 (7.1–44.2)	79.5

CTG, cardiotocography; PTB, preterm birth.

to TTTS or growth restriction, while 62.8% (95% CI, 34.0–87.4%; $I^2 = 31.0\%$) were unexpected. The corresponding figures for cases managed mainly as outpatients were 12.0% (95% CI, 4.1–23.2%; $I^2 = 0\%$) and 69.3% (95% CI, 46.7–87.9%; $I^2 = 32.8\%$).

Finally, the rate of delivery ahead of schedule was explored. Overall, 37.8% (95% CI, 28.0–48.2%) of MCMA pregnancies were delivered before the scheduled time, due mainly to spontaneous preterm labor or abnormal CTG findings. In MCMA twin pregnancies scheduled for delivery at 32 weeks of gestation, the rate of delivery before this time was 18.5% (95% CI, 6.5–34.8%), while the corresponding figure for those scheduled between 32 and 34 weeks was 34.7% (95% CI, 26.6–43.2%) (Table 5). When stratifying the analysis according to the type of prenatal management adopted, the risk of unexpected delivery was 44.9% (95% CI, 28.7–61.6%) and 42.3% (95% CI, 26.4–59.4%) in pregnancies managed mainly as inpatients and those managed mainly as outpatients, respectively. In pregnancies managed mainly as inpatients, 22.7% (95% CI, 10.3–38.2%) and 44.9% (95% CI, 28.7–61.6%) of unexpected deliveries were due to preterm birth and CTG abnormalities, respectively, while the corresponding figures for pregnancies managed mainly as outpatients were 16.4% (95% CI, 10.4–23.4%) and 16.7% (95% CI, 5.9–31.4%).

DISCUSSION

Main findings

The findings of this systematic review show that the overall incidence of fetal loss in MCMA pregnancies is approximately 6%. The large majority of fetal losses occurred before 30 weeks of gestation, while the risk of demise at 31–32 and 33–34 weeks of gestation was 1% and 2%, respectively. Most IUDs were unexpected, thus questioning the optimal type of assessment in these pregnancies. Finally, the incidence of fetal loss in twins of pregnancies managed mainly as inpatients was 3% as compared with 7% in those followed up as outpatients. Despite this, the heterogeneity in the type of prenatal assessment among the included studies highlights the need for developing an adequate protocol for prenatal management of MCMA twin pregnancies, focusing on the type and frequency of follow-up rather than admission to the hospital.

Strengths and limitations

The small number of cases in some of the included studies, their retrospective non-randomized design, dissimilarity of the populations (due to varied inclusion criteria) and lack of standardized criteria for the antenatal management of MCMA twin pregnancies represent the major limitations of this systematic review. Assessment of potential publication bias was also problematic because of the nature of the outcome evaluated (outcome rates, with the left-side limited to a value of zero), which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits the reliability of formal tests. Another major limitation of this systematic review is represented by differences in the antenatal management of MCMA pregnancies in terms of type and frequency of assessment. Despite these limitations, the present review represents the most comprehensive published estimate of the investigated outcomes in MCMA twin pregnancies.

Implications for clinical practice

Management of MCMA twin pregnancy is challenging. As there are no randomized trials assessing the optimal prenatal management of MCMA pregnancies in terms of type and frequency of follow-up and gestational age at delivery, it is not possible to provide specific recommendations on how to manage these pregnancies.

It is true that MCMA twins are rare; however, prenatal identification of those pregnancies is fundamental in their risk stratification and tailoring their antenatal care[4].

In the present systematic review, only 30% of IUDs were due to recognizable conditions such as TTTS or growth abnormalities, while the large majority of them occurred unexpectedly. However, prenatal diagnosis of TTTS in MCMA twin pregnancy is challenging and not based upon classical ultrasound features observed in these pregnancies. Polyhydramnios and non-visualization of the bladder in one of the twins are usually the first signs of TTTS in MCMA twin pregnancy. In this scenario, it may be entirely possible that some of the fetal losses labeled as unexpected were the result of undiagnosed TTTS. This highlights the need for thorough regular examination of MCMA twins in order to look for signs of TTTS, such as amniotic fluid volume, visualization of the bladder and fetal Doppler.

Timing of delivery of apparently uncomplicated MCMA twins is still debated. It is common practice to deliver MCMA twins between 32 and 34 weeks of gestation, in view of the reported high risk of IUD in the third trimester of pregnancy. However, most of the previously published studies included fetuses with anomalies, which are at higher risk of fetal loss, and come from an era in which the natural history of TTTS had not been systematically elucidated, thus explaining the high rate of deaths labeled as unexpected in otherwise apparently uncomplicated MCMA twins.

The findings of this review showed that fetal loss occurs in 1% of MCMA twins at 31–32 weeks and 2% at 33–34 weeks of gestation; furthermore, double fetal demises affected about 2% of twins at 33–34 weeks of gestation, thus highlighting the need for a thorough follow-up if the pregnancy is continued beyond 32 weeks. A policy of elective delivery at 32 weeks of gestation may look appropriate in view of the apparently higher risk of fetal demise occurring later on in gestation, but should be balanced against the potentially higher risk of neonatal morbidity. However, a large proportion of MCMA twins will be delivered before the scheduled time, especially as a consequence of spontaneous preterm labor.

The type of prenatal follow-up of MCMA twin pregnancy is also controversial. Some studies claim that elective admission to the hospital in the third trimester may improve the outcome of MCMA pregnancy, while others have shown no difference. Furthermore, there is as yet no consensus on when to start intensive follow-up and monitoring.

In the present systematic review, the incidence of fetal loss was 3% in twins of pregnancies managed mainly as inpatients compared with 7% in those of pregnancies followed up as outpatients. However, there was significant heterogeneity in the management protocols among the included studies, which might have biased the results. Furthermore, comparison between inpatient and outpatient monitoring was affected by the largest study included in the analysis[16]. In that study, outpatient surveillance was started at 30 weeks for the majority of included centers, whereas inpatient surveillance was started at 24 weeks. Deaths in the outpatient group occurred before 30 weeks (i.e. before initiation of surveillance), while after 30 weeks, the number of deaths in the inpatient and outpatient cohorts was very similar (1.4 *vs* 2.4%).

The perinatal outcome of MC pregnancies is dependent not only on the degree of placental sharing between the twins but also on the direction and the magnitude of blood flow through the intertwin anastomoses. MCMA twins have a lower risk of developing TTTS compared with MCDA pregnancies due to their peculiar vascular arrangement with nearby placental insertions of the umbilical cords and the large arterioarterial anastomoses. However, acute unpredictable transfusion events can still occur[3].

An adequate prenatal management of monoamniotic twins should include serial assessment of the amniotic fluid, fetal urinary bladders and Doppler studies to rule out signs of TTTS. It is unclear whether systematic evaluation of umbilical cords to diagnose entanglement may reduce the risk of fetal loss, as many of them are acute events that may not be easily predicted. Regarding the frequency of fetal monitoring, a twice-weekly scan starting from 24–26 weeks of gestation has been proposed in view of the high rate of perinatal loss occurring at 24–30 weeks of gestation. Despite this, parental counseling should stress the fact that a normal scan cannot completely rule out adverse events, as they may occur acutely.

Further large studies are needed in order to develop objective protocols for antenatal surveillance of MCMA twins, aiming at reducing the risk of perinatal mortality and morbidity in these pregnancies. Considering the occurrence of IUD in the subgroups of MCMA pregnancies managed as inpatients and those managed as outpatients (3.02% and 7.40%, respectively), a minimum of 806 (403 per group) pregnancies would be needed to find a difference in mortality according to the two management options, with a power of 80% and an alpha error of 0.05.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Search strategy for articles on outcome of monochorionic monoamniotic twin pregnancy

Table S2 Excluded studies and reason for exclusion

This article has been selected for Journal Club.

A slide presentation prepared by Dr Yael Raz, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Shuang Liu and Prof. Qingqing Wu, ISUOG China Task Force.
Spanish translation by Dr Rubén D. Fernández Jr.

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Mortalidad perinatal, momento del parto y tratamiento prenatal del embarazo gemelar monoamniótico: revisión sistemática y metaanálisis

RESUMEN

Objetivo Cuantificar la tasa de mortalidad perinatal en los embarazos gemelares monocoriónicos monoamnióticos (MCMA), en función de la edad gestacional, y determinar la incidencia de la mortalidad en los embarazos atendidos en pacientes hospitalizadas en comparación con los atendidos en pacientes ambulatorias.

Métodos Se realizaron búsquedas en las bases de datos de MEDLINE, EMBASE y CINAHL dirigidas a estudios sobre embarazo gemelar monoamniótico. Las medidas de resultados primarios examinadas fueron (todas las siglas del inglés) la incidencia de muerte intrauterina (IUD), la muerte neonatal (NND) y la muerte perinatal (PND) en gemelos MCMA en diferentes edades gestacionales (24–30, 31–32, 33–34, 35–36 y ≥ 37 semanas de gestación). Las medidas de resultados secundarios fueron la incidencia de IUD, NND y PND en los gemelos MCMA según el tipo de monitorización fetal (paciente hospitalizada frente a paciente ambulatoria) y la incidencia de parto pretérmino. Para analizar los datos se utilizaron metaanálisis de modelo de efectos aleatorios.

Resultados Se incluyeron 25 estudios (1628 gemelos no anómalos que alcanzaron las 24 semanas de gestación). Las muertes intrauterinas simples (sIUD) y dobles (dIUD) ocurrieron en el 2,5% (IC 95%: 1,8–3,3%) y el 3,8% (IC 95%: 2,5–5,3%) de los casos, respectivamente. La IUD ocurrió en el 4,3% (IC 95%: 2,8–6,2%) de los gemelos a las 24–30 semanas de gestación, en el 1,0% (IC 95%: 0,6–1,7%) a las 31–32 semanas y en el 2,2% (IC 95%: 0,9–3,9%) a las 33–34 semanas, mientras que no hubo ningún caso de IUD, ya fuera simple o doble, a partir de las 35 semanas de gestación. En los embarazos gemelares MCMA tratados principalmente como pacientes hospitalizadas, la incidencia de la IUD fue del 3,0% (IC 95%: 1,4–5,2%), mientras que la cifra correspondiente para las que se trataron principalmente como pacientes ambulatorias fue del 7,4% (IC 95%: 4,4–11,1%). Finalmente, el parto del 37,8% (IC 95%, 28,0–48,2%) de los embarazos MCMA fue antes del momento programado, debido principalmente a parto pretérmino espontáneo o a hallazgos anómalos en la CTG.

Conclusiones Los gemelos MCMA tienen un alto riesgo de pérdida perinatal durante el tercer trimestre del embarazo, y la gran mayoría de estas pérdidas ocurren como eventos aparentemente inesperados. El tratamiento hospitalario parece estar asociado con una menor tasa de mortalidad, aunque se necesitan estudios adicionales para establecer el tipo y el momento adecuado de la evaluación prenatal en estos embarazos.

围产期死亡率、分娩时间与单羊膜双胎妊娠产前处理：系统评估与元分析

摘要

目的：根据产妇孕龄进行单绒毛膜单羊膜（MCMA）双胎妊娠围产期死亡率量化处理，并对照门诊管理孕妇与住院管理孕妇确定两者的妊娠死亡率。

方法：检索了 MEDLINE、EMBASE 和 CINAHL 数据库中的单羊膜双胎妊娠研究项目。检索中发现的主要结果是不同孕龄窗口（24 – 30 周、31 – 32 周、33 – 34 周、35 – 36 周及 37 周或以上的妊娠期）MCMA 双胎的宫内死亡（IUD）、新生儿死亡（NND）与围产期死亡（PND）发生率。次要结果是根据胎儿监护类型（住院与门诊）分类的 MCMA 双胎 IUD、NND 与 PND 发生率，以及早产发生率。采用了随机效应模型元分析法分析数据。

结果：纳入 25 个研究项目（1628 个 24 周孕期的非异常双胞胎）。单胎(sIUD)与双胎(dIUD)宫内死亡发生率分别为全部案例的 2.5% (95% CI, 1.8-3.3%) 与 3.8% (95% CI, 2.5-5.3%)。24 – 30 周孕期双胎 IUD 发生率为 4.3% (95% CI, 2.8 – 6.2%)，31 – 32 周孕期为 1.0% (95% CI, 0.6 – 1.7%)，33 – 34 周孕期为 2.2% (95% CI, 0.9 – 3.9%)，35 周孕期单胎或双胎案例的 IUD 均为零。在主要进行住院管理的 MCMA 双胎孕妇中，IUD 发生率为 3.0% (95% CI, 1.4 – 5.2%)，而在主要进行门诊管理的孕妇中，这一数据为 7.4% (95% CI, 4.4 – 11.1%)。最后一点，37.8% (95% CI, 28.0 – 48.2%)的 MCMA 孕妇是早产案例，主要原因是自发性早产或 CTG 异常发现。

结论：MCMA 双胎妊娠晚期围产期死亡发生率较高，此类死亡中绝大部分明显属于意外事件。住院管理似乎与围产期死亡率较低有关联，虽然还需要进行后续研究来确定这些妊娠案例中产前评估的适当类型与时间。