Prospective risk of stillbirth and neonatal complications in twin pregnancies: A systematic review and meta-analysis

Fiona Cheong-See
Clinical Research Fellow
Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, 58 Turner Street, United Kingdom E1 2AB

Ewoud Schuit
Postdoctoral Research Fellow
Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands
Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam, The Netherlands
Stanford Prevention Research Center, Stanford University, 1265 Welch Rd, Palo Alto, Stanford, CA 94305

David Arroyo-Manzano
Biostatistician
Clinical Biostatistics Unit, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Ctra. Colmenar Viejo, km. 9100 28034, Madrid, Spain

Asma Khalil
Consultant Obstetrician
Fetal Medicine Unit, St George's Healthcare NHS Trust, London, United Kingdom SW17 0QT

Jon Barrett
Senior Scientist
Evaluative Clinical Sciences, Women & Babies Research Program, Sunnybrook Research Institute, 2075 Bayview Ave, Toronto, ON M4N 3M5, Canada

KS Joseph
Professor of Obstetrics & Gynaecology
Department of Obstetrics & Gynecology, University of British Columbia, 1190 Hornby Street - 4th Floor, Vancouver, BC Canada V6Z 2K5

Elizabeth Asztalos
Associate Professor
Department of Newborn & Developmental Paediatrics, Women & Babies Research Program, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Toronto, ON M4N 3M5, Canada

Karien Hack
MD and PhD in Obstetrics & Gynaecology

*Department of Gynaecology and Obstetrics, Diakonessenhuis, Bosboomstraat 1
3582 KE Utrecht, The Netherlands*

Liesbeth Lewi
*Assistant Professor in Obstetrics & Gynaecology
Department of Obstetrics-Gynecology, University Hospitals, Herestraat 49
3000 Leuven, Belgium
Department of Development and Regeneration: Pregnancy, Fetus and Neonate, KU
Leuven, Belgium*

Arianne Lim
*Gynaecologist
Department of Obstetrics & Gynaecology, Academic Medical Center, Meibergdreef 9,
1105 AZ Amsterdam, The Netherlands*

Sophie Liem
*MD in Obstetrics & Gynaecology
Department of Obstetrics & Gynaecology, Academic Medical Centre, Meibergdreef 9,
1105 AZ Amsterdam, The Netherlands*

Jane E Norman
*Professor of Maternal and Fetal Health
University of Edinburgh MRC Centre for Reproductive Health, The Queen's Medical
Research Institute, Edinburgh, United Kingdom EH16 4TY*

John Morrison
*Professor of Obstetrics & Gynaecology and Pediatrics
Department of Obstetrics & Gynecology, University of Mississippi Medical Center,
Jackson, USA*

C Andrew Combs
*Associate Director of Research
Obstetrix Collaborative Research Network, The Center for Research, Education and
Quality, Mednax National Medical Group, 1301 Concord Terrace, Sunrise, Florida
33323, USA*

Thomas J Garite
*Professor Emeritus of Obstetrics & Gynaecology, University of California Irvine, Irvine,
California 92697 USA
Director of Research & Education, Obstetrix Collaborative Research Network, The
Center for Research, Education and Quality, Mednax National Medical Group, 1301
Concord Terrace, Sunrise, Florida 33323, USA*

Kimberly Maurel
Associate Director

Obstetrix Collaborative Research Network, The Center for Research, Education and Quality, Mednax National Medical Group, 1301 Concord Terrace, Sunrise, Florida 33323, USA

Vicente Serra
Professor of Obstetrics & Gynaecology
Maternal-Fetal Medicine Unit, Instituto Valenciano de Infertilidad, University of Valencia, Spain; Department of Obstetrics & Gynaecology, Faculty of Medicine, University of Valencia, Jefe Servicio Obstetricia Hospital U P La FE, Torre F, planta 3a, Bulevar Sur s/n 46026 Valencia, Espana

Alfredo Perales
Professor of Obstetrics & Gynaecology
Department of Obstetrics, University Hospital La Fe, Valencia, Calle Fernando Abril Martorell, 106, 46026 València Spain; Department of Obstetrics & Gynaecology, Faculty of Medicine, University of Valencia.

Line Rode
Senior Resident
Center of Fetal Medicine, Department of Obstetrics, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark

Katharina Worda
Specialist in Obstetrics & Gynaecology
Department of Obstetrics & Gynecology, Medical University of Vienna, Spitalgasse 23, 1090 Wien, Austria

Anwar Nassar
Professor of Obstetrics & Gynaecology
Department of Obstetrics & Gynecology, American University of Beirut Medical Center, Riad El Solh, Beirut 1107 2020, Lebanon

Mona Aboulghar
Professor of Obstetrics & Gynaecology
The Egyptian IVF Center, Maadi and Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Cairo University Road, Oula, Giza, Egypt

Dwight Rouse
Principal Investigator for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Research Network and Professor of Obstetrics & Gynaecology
Department of OB/GYN, Women and Infants Hospital, Brown University Women and Infants Hospital, 101 Dudley Street, Providence, Rhode Island, 02905 USA

Elizabeth Thom
Research Professor of Biostatistics & Epidemiology

The Biostatistics Center, George Washington University, 6110 Executive Blvd #750, Rockville, MD 20852, USA

Fionnuala Breathnach
Consultant Obstetrician & Gynaecologist , Senior Lecturer in Maternal Fetal Medicine
Royal College of Surgeons in Ireland, Rotunda Hospital, Parnell Square, Dublin, Ireland

Soichiro Nakayama
Assistant Professor
Department of Maternal Fetal Medicine, Osaka Medical Center and Research Institute for Maternal and Child Health, 840, Murodocho, Izumi, Osaka, Japan, Zip Code 594-1101

Francesca Maria Russo
MD in Obstetrics & Gynaecology
Department of Obstetrics & Gynecology, University of Milano-Bicocca, Piazza dell'Ateneo Nuovo, 1, 20126 Milano, Italy

Julian N Robinson
Chief of Obstetrics and Associate Professor
Division of Maternal Fetal Medicine, Department of Obstetrics & Gynecology, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115, USA

Jodie M. Dodd
Professor of Obstetrics & Gynaecology
The The Robinson Research Institute, and Discipline of Obstetrics & Gynaecology, The University of Adelaide, 72 King William Road, North Adelaide SA 5006, Australia

Roger B Newman
Professor and Maas Chair for Reproductive Sciences
Department of Ob-Gyn, Medical University of South Carolina, 165 Cannon St # 503, Charleston, South Carolina 29403, USA

Sohinee Bhattacharya
Senior Lecturer
University of Aberdeen
Dugald Baird Centre for Research on Women's Health, Aberdeen Maternity Hospital, Cornhill Road, Aberdeen AB25 2ZL, Scotland

Selphee Tang
Data Analyst
Department of Obstetrics and Gynecology, Alberta Health Services, 4th Floor, North Tower, Foothills Medical Centre, 1403-29 Street NW, Calgary, Alberta T2N 2T9 Canada

Ben Willem J. Mol

Professor of Obstetrics & Gynaecology
Australian Research Centre for Health of Women and Babies, Robinson Institute, The University of Adelaide, 72 King William Road, North Adelaide SA 5006, Australia

Javier Zamora
Head of Clinical Biostatistics Unit, Director of Clinical Epidemiology Research Area
Clinical Biostatistics Unit, Hospital Ramón y Cajal (IRYCIS), Ctra. Colmenar Viejo, km. 9100 28034, Madrid, Spain
CIBER Epidemiology and Public Health (CIBERESP), Madrid, Spain

Senior Lecturer
Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, 58 Turner Street, London E1 2AB, United Kingdom

Basky Thilaganathan*
Professor and Director of Fetal Medicine
Fetal Medicine Unit, St George's Healthcare NHS Trust, London SW17 0QT United Kingdom

Shakila Thangaratinam*
Professor of Maternal and Perinatal Health
Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, 58 Turner Street, London E1 2AB, United Kingdom

*joint last authors

A Global Obstetrics Network (GONet) Collaboration

Author for Correspondence
Javier Zamora
Clinical Biostatistics Unit
Hospital Ramón y Cajal (IRYCIS)
Ctra. Colmenar Viejo, km. 9100 28034,
Madrid, Spain
Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, 58 Turner Street, London E1 2AB, United Kingdom

E Mail: javier.zamora@hrc.es Ph: +34 913368103

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ABSTRACT

Study question

What are the risks of stillbirth and neonatal complications by gestational age in uncomplicated monochorionic and dichorionic twin pregnancies?

Methods

We searched Medline, Embase and Cochrane databases (until December 2015) without language restrictions for studies of women with uncomplicated twin pregnancies, which reported rates of stillbirth and neonatal outcomes at various gestational ages. We excluded pregnancies with unclear chorionicity, monoamnionicity and twin-to-twin transfusion syndrome. Meta-analyses of observational studies and cohorts nested within randomised studies were undertaken. We computed prospective risk of stillbirth for each study at a given week of gestation, and compared with the risk of neonatal death amongst deliveries in the same week. We estimated the gestational age-specific risk differences for stillbirths and neonatal deaths in monochorionic and dichorionic twin pregnancies after 34 weeks of gestation.

Study answer and limitations

Thirty-two studies (29,685 dichorionic, 5,486 monochorionic pregnancies) were included. In dichorionic twin pregnancies beyond 34 weeks (15 studies, 17,830 pregnancies), the prospective weekly risk of stillbirths from expectant management and the risk of neonatal death from delivery were balanced at 37 weeks' gestation (risk difference 1.2/1000; 95% CI -1.3 to 3.6, $I^2 = 0\%$). Delay in delivery by a week (until 38 weeks) led to an additional 8.8 perinatal deaths per 1000 pregnancies (95% CI 3.6 to

14.0 /1000, $I^2 = 0\%$) compared to previous week. In monochorionic pregnancies beyond 34 weeks (13 studies, 2,149 pregnancies), there was a trend towards increase in stillbirths than neonatal deaths after 36 weeks, with an additional 2.5 per 1000 perinatal deaths, which was not significant (95% CI -12.4 to 17.4/1000, $I^2 = 0\%$). The rates of neonatal morbidity showed a consistent reduction with increasing gestational age in mono and dichorionic pregnancies, and admission to the neonatal intensive care unit was the commonest neonatal morbidity. The actual risk of stillbirth near term may be higher than reported estimates due to the policy of planned delivery in twin pregnancies.

Conclusions

In order to minimise perinatal deaths, delivery should be offered at 37 weeks' gestation in uncomplicated dichorionic twin pregnancies, and considered at 36 weeks in monochorionic pregnancies.

Systematic review registration

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INTRODUCTION

Twin pregnancies are high risk, with a thirteen-fold increase in stillbirth rates in monochorionic, and a five-fold increase in dichorionic twins, compared to singleton pregnancies.[1-3] Uncomplicated twin pregnancies are often delivered early in an attempt to prevent late stillbirth. Delivery before term predisposes to prematurity-associated neonatal complications.[1] Since 2005, the number of patient safety incidents involving multiple pregnancies, including unexpected stillbirth and neonatal deaths, has risen by 419% in UK, and peaked in 2013/14, resulting in payouts of over £90 million.[4,5] The optimal gestational age for delivery that minimises fetal and neonatal complications in twin pregnancies is not known. Current recommendations vary on the timing of delivery, starting from 34 until 37 weeks' gestation in monochorionic,[6] and from 37 to 39 weeks in dichorionic twin pregnancies.[7-10]

Women and their partners, clinicians, and guideline makers need robust estimates of stillbirth risk from continuing the pregnancy, and neonatal risk from early delivery, to decide on the optimal timing of delivery. Existing reviews have focused mainly on stillbirth risk without taking into account the neonatal outcomes.[11] There are no published data on gestation and chorionicity specific perinatal mortality and morbidity in twins to guide decision-making on the timing of delivery.[12] Furthermore, randomised trials on timing of delivery in twins are not adequately powered to provide robust estimates of benefit.[13,14]

We summarised data from individual studies to quantify the prospective risks of stillbirth in women with uncomplicated monochorionic and dichorionic twin

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pregnancies, as well as the risks to the newborn, when delivered after 34 weeks' gestation, and at various gestational ages,.

METHODS

We conducted the systematic review based on a prospective protocol[15] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Appendix 1).[16]

Identification of studies

We searched the major electronic databases Medline, Embase and Cochrane Library using the NHS Evidence website and Cochrane online library platforms from inception until December 2015 for studies on twin pregnancies reporting rates of stillbirth. Search terms representing the participants ('monochorionic' OR 'dichorionic' OR 'twin pregnancy' OR 'multiple pregnancy') were combined with outcome terms ('stillbirth' OR ('fetal or foetal or fetus or foetus' AND 'death or demise or mortality')). We supplemented this search with an added search for neonatal outcomes in twin pregnancies (Appendix 2). We searched the reference lists of included studies. There were no language restrictions. Additionally, we contacted individual authors members of the collaborative research networks such as Global Obstetric Network (GONet),[17] Evidence Based Medicine Connect (EBM Connect)[18], and the Twin pregnancies Individual Participant Data (IPD) Meta-Analysis group for relevant data.[19]

Study selection

Two independent reviewers (FCS and ES) selected the studies by a two-stage process. In the first stage, the abstracts and titles of citations were assessed for their eligibility. In the second stage, we obtained the full texts of the studies that appeared to fulfill the inclusion criteria for evaluation.

We included both observational cohort studies and cohorts nested in randomised studies on rates of stillbirth or neonatal outcomes in monochorionic and/or dichorionic twin pregnancies. We excluded studies with the following characteristics: unclear chorionicity, monoamnionicity, unable to exclude twin-to-twin transfusion syndrome in fetuses, and outcomes not provided in weekly or two weekly gestational periods.

We defined stillbirth as a baby born without signs of life after the viability age, or any other definition used by the authors. Neonatal mortality was defined as neonatal death up to 28 days from delivery. For infants born after 34 completed weeks of gestation, we considered the following morbidity outcomes to be clinically relevant: need for assisted ventilation, respiratory distress syndrome (RDS), septicemia, hypoxic ischaemic encephalopathy or neonatal seizures, and admission to the neonatal intensive care unit. For preterm infants, born between 26 and 33^{+6} weeks' gestation, in addition to the above, we assessed the rates of bronchopulmonary dysplasia, necrotising enterocolitis, significantly abnormal cranial ultrasound scan (cystic periventricular leukomalacia or grade 3 or 4 intraventricular hemorrhage), and retinopathy of prematurity (stages 3 to 5) (Appendix 3).

Quality assessment and data extraction

Two independent reviewers (FCS and ES) evaluated the quality of the studies by investigating separate parameters for the internal validity (the extent to which the information is probably free from bias) and external validity (the representativeness of the population). [20-22] We evaluated individual parameters such as study design, method of sampling, adequacy of follow-up, ascertainment of the outcome, and appropriate determination of gestational age, and chorionicity for internal validity. Studies with features such as prospective design, consecutive or random recruitment of patients, follow-up rates of over 80%, and use of first trimester ultrasound signs to determine chorionicity and gestational age were considered to have low risk of bias. Studies without these features or with unclear reporting were classified to have high risk of bias. We categorised the studies with the following criteria to be highly representative for external validity: clear definition of uncomplicated twin pregnancies, exclusion of pregnancies where one or both of the babies were diagnosed antenatally with growth restriction or major congenital abnormalities. Any discrepancies were resolved after discussion with a third reviewer (ST).

Analysis

We undertook separate analyses for risks of stillbirth and neonatal complications in monochorionic and dichorionic twin pregnancies in two periods: from 34 weeks' gestation and beyond, and early preterm (<34 weeks) gestation. From 34 weeks onwards, we estimated the risks by weekly gestational ages, with the 34-week period representing pregnancies entering the 34^{+0} to 34^{+6} weeks' gestation with live fetuses, and so forth. For early preterm (<34 weeks) gestation, we estimated risks of outcomes by two weekly intervals.

We computed the weekly prospective risk of stillbirth by dividing the number of stillbirths observed at that week by the number of women at risk in the same week. For a given gestational age, we defined women at risk of stillbirth as those who were still pregnant at the beginning of the week. We corrected for deliveries in that week by subtracting half the number of women who delivered that week.[23] For risk of neonatal death, we used a similar approach and divided the number of neonatal deaths observed to the number of deliveries at that week.

In pregnancies beyond 34 weeks' gestation, we assessed the competing risks of expectant management versus delivery at a particular gestational age, for each study. We defined the risk of perinatal death at a given gestational week as the difference between stillbirth and neonatal death risk for deliveries in that week. This provided a direct measure of benefit or harm from expectant management vs. immediate delivery strategy. A risk difference ≤ 0 indicates a reduction in risk of perinatal death with expectant management at that gestational age, compared with immediate delivery. We pooled risk differences from individual studies using a fixed effect model weighted by the inverse of its variance. We computed I-squared as an estimation of between-study heterogeneity and assumed values lower than 50% as little heterogeneity and I-squared greater than 75% as substantial heterogeneity.

We estimated the weekly risk of neonatal outcomes by fitting multi-level random effects logistic regression models with gestational age as the unique categorical independent variable. The units of the analysis were pregnancies (first level) that were clustered within studies (second level of the analysis). We obtained point estimates of

the risk of each event by the gestational period along with its corresponding 95% confidence interval (CI). We planned prior to analysis to restrict our evaluation up to the gestational week for which robust, unbiased data were available.

Sensitivity analysis was planned before analysis to exclude studies involving pregnancies complicated by congenital abnormalities, and those with low external validity. We assessed publication bias and small studies effect using funnel plots representing overall event rate (in logit scale) versus its standard error. We used Begg's[24] and Egger's[25] tests to assess funnel asymmetry.

RESULTS

Identification of studies

From 2574 citations, we included 32 studies reporting on 35,171 women with twin gestations (Figure 1).[14,26-53] Eighteen studies provided data on both monochorionic and dichorionic,[14,28,30,32,34,36,38,40-43,46-49,52,54,55] seven on only monochorionic,[27,29,35,37,39,45,51] and seven on only dichorionic twin pregnancies.[26,31,33,44,50,53,56] Twenty-three authors provided relevant unpublished data.[14,26,28,30-33,36,37,39-41,45-52,54-56]

Characteristics and quality of the included studies

Fifteen studies on dichorionic pregnancies (17,830 women), and 13 on monochorionic pregnancies (2,149 women) provided weekly stillbirth data after 34 weeks' gestation. The corresponding neonatal death rates were provided by 13 (n=10,333) studies for dichorionic, and 11 (n=1,461) for monochorionic pregnancies. Overall, 14 studies excluded pregnancies complicated by fetal growth restriction, and 28 studies excluded

pregnancies with major congenital abnormalities. The diagnosis of fetal growth restriction and congenital abnormalities were made antenatally. The postmortem findings of the stillborn babies were reviewed for evidence of growth restriction in two studies. There were no major differences between the studies in the definitions of stillbirths, neonatal mortality, and morbidity outcomes (Appendix 3).

The qualities of the studies were adequately representative in 27 (27/32, 84%), and inadequately or unclearly representative in 5 (5/32, 16%) (Figure 2). Fifteen of the included studies (15/32) were prospective, and of these 12 (12/32, 38%) were nested cohorts in randomised trials. Most studies used random or consecutive sampling methods (31/32, 97%), achieved adequate follow-up (26/32, 81%), and had low ascertainment bias in determining stillbirth outcome (31/32, 97%). Twenty studies had a low risk of misclassification bias for gestational age assessment (20/32, 63%), and chorionicity determination (25/32, 78%).

Stillbirth and neonatal mortality beyond 34 weeks' gestation

Dichorionic twin pregnancies

The prospective risk of stillbirth was 1.2 per 1000 pregnancies (95% CI 0.7-1.8) at 34^{+0-6} weeks, with the corresponding risk of neonatal death of 6.7 per 1000 pregnancies (95% CI 3.3 to 13.5) (Table 1). The risks of stillbirth were significantly lower than the risks of neonatal deaths at 34^{+0-6} (risk difference -5.8/1000, 95% CI -10.4 to -1.2/1000, $I^2=0\%$), and 35^{+0-6} weeks' gestation (risk difference -5.1/1000, 95% CI -8.7 to -1.6/1000, $I^2=0\%$). The perinatal risks were balanced at 37^{+0-6} weeks (risk difference 1.2/1000, 95% CI -1.3 to 3.6/1000, $I^2=0\%$), beyond which the stillbirth risks (10.6, 95% CI 7.1 to

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15.3) significantly outweighed the neonatal death risk (1.5/1000, 95% CI 0.7 to 3.3) from delivery (risk difference 8.8/1000, 95% CI 3.6 to 14/1000, I^2=0%) (Figure 3). Analysis by excluding fetuses with congenital abnormalities showed results similar to the main analysis (Appendix 6). Exclusion of studies with low external validity showed a trend towards increased stillbirth risk than neonatal death beyond 37^{0+6} weeks, which was not statistically significant.

Monochorionic twin pregnancies

At 34 weeks, the prospective risk of stillbirth and neonatal mortality rates in monochorionic pregnancies were 0.9 (95% CI 0.1 to 3.4) and 12.1 (95% CI 4.2 to 34.3) respectively. The risks of neonatal death were higher than stillbirth at 34^{+0-6} (risk difference -15.6/1000, 95% CI -40.4 to 9.1/1000, I^2=0%) and 35^{+0-6} weeks (risk difference -2.4/1000, 95% CI -17.6 to 12.8/1000, I^2=0%) which were not statistically significant (Figure 3). Beyond 36^{+0-6} weeks, we observed a trend where the risk of stillbirth (9.6/1000, 95% CI 3.9 to 19.7) was higher than neonatal deaths (3.6/1000, 95% CI 1.2 to 11.1) with a risk difference of 2.5/1000 (95% CI -12.4 to 17.4/1000, I^2=0%). Sensitivity analysis by excluding studies with congenitally malformed fetuses (Appendix 6), and studies with low external validity showed similar findings.

All analyses were restricted until 38 weeks for monochorionic twin pregnancies and until 39 weeks for dichorionic twin pregnancies due to the non-availability of robust data beyond this period.

Neonatal morbidity beyond 34 weeks' gestation

We observed a consistent and significant reduction in the rates of assisted ventilation, respiratory distress syndrome, admission to neonatal intensive care unit, and septicaemia with increasing gestational age in babies of both monochorionic and dichorionic twin pregnancies (Table 2). Neonatal Intensive Care Unit (NICU) admission in the infants was the commonest complication in monochorionic and dichorionic twin pregnancies.

Stillbirth and neonatal outcomes in early preterm twin pregnancies

The cumulative risks of stillbirth and risks of neonatal deaths by two weekly gestational periods in early preterm twin pregnancies (between 26 to 33 weeks and 6 days gestation) are provided in Appendix 4. Early preterm neonatal outcomes in two-weekly epochs are shown in Appendix 5. Neonatal morbidity reduced with increasing gestational age in all twin pregnancies. The commonest neonatal complications were respiratory distress syndrome, septicaemia, admission to the neonatal intensive care unit (NICU) and need for assisted ventilation, in both monochorionic and dichorionic pregnancies.

Publication bias and small studies effect

Funnel plots found a slight asymmetry for stillbirth outcome in monochorionic pregnancies. Smaller studies tended to show lower stillbirth rates than larger studies (Begg's test p-value = 0.139 and Egger's test p-value = 0.014). We did not find evidence of publication bias for other outcomes

DISCUSSION

Our study provides comprehensive estimates comparing risks of stillbirth, and neonatal mortality at various gestational ages, which is required for planning delivery in uncomplicated twin pregnancies. In dichorionic twin pregnancies the perinatal risks are balanced until 37^{0+6} weeks' gestation, and until 36^{0+6} in monochorionic pregnancies, with higher risks of stillbirths than neonatal deaths beyond this gestation.

We have undertaken the largest and most robust systematic review to-date on stillbirths and neonatal outcomes in twin pregnancies. In addition to the stillbirth risk at each gestational week, we provided risk estimates of the other equally important consequence of early delivery, namely neonatal death. Ours is the first review to provide chorionicity and gestational age-specific neonatal morbidity estimates in twin pregnancies. All the included studies were relatively recent and published within the last ten years. The sharing of unpublished aggregate and individual patient data by authors enabled us to provide our findings in clinically relevant weekly intervals. We chose the gestational timeframes to reduce bias from varied lengths of follow up. We minimised heterogeneity by excluding studies without clear details on twin-to-twin transfusion syndrome. Our sensitivity analyses allowed us to assess the risks in pregnancies not complicated by congenital malformation, and by fetal growth restriction.

Our findings were limited by the policy of planned delivery beyond 37 and 38 weeks gestation in most studies. This reduced the available sample size near term, particularly in monochorionic pregnancies, and may have underestimated the risk of stillbirth in the last epoch. Although we observed an increased prospective risk of stillbirth than neonatal death beyond 36 weeks in monochorionic pregnancies, the differences were not statistically significant. This was due to the gradual decline in the number of

pregnancies available for analysis, which may be attributed to the policy of elective delivery near term. Most studies did not provide details on whether stillbirth was diagnosed antenatally or at birth. However, given the policy of regular ultrasound for fetal monitoring in most units, we expect the interval between diagnosis and delivery to be small. The variation observed in the clinical management of twin pregnancies and neonatal care after delivery between centres may also have influenced the outcomes.[57] The small study effects that we observed for stillbirth outcomes in monochorionic pregnancies could be attributed to selective reporting or publication of data from centres showing good outcomes and small sample sizes. We ensured that all data were available from 34 weeks for women in randomised trials, but it is possible that women with early stillbirth would not be in the analysis.

We have taken a pragmatic approach by including all twin pregnancies not complicated by twin-to-twin transfusion syndrome. We were not able to provide separate estimates for individual causes of neonatal mortality, or for elective and emergency deliveries. The results did not vary after excluding pregnancies complicated by fetal growth restriction, one of the main indications for emergency delivery. We only focused on short-term neonatal morbidity due to paucity of data.[58,59] We provided the risk estimates per pregnancy and not per fetus, as it is likely that mothers would consider the prospective risk of death in either of their fetuses *in utero* or after delivery to be equally important. However, this limited our ability to distinguish between those pregnancies with a single or double adverse outcome.

Primary studies,[13,14,27,37,60] systematic reviews,[11] and guideline bodies[7,61] were limited in their interpretation of evidence on the timing of delivery in twin pregnancies due to paucity of data and methodological inadequacies. Firstly, they compared the risks of stillbirth in twin pregnancies at various gestational weeks with those at (or) near term, without considering the inherent longitudinal design with women repeatedly observed during the pregnancy.[62] Secondly, some studies made risk estimations using survival analysis (Kaplan-Meier method). Delivery was not considered as a competing event for the outcome of stillbirth, and may have overestimated the risk.[63] Thirdly, studies did not provide gestational age-specific pooled estimates for significant neonatal morbidity.[11,64] Fourthly, existing recommendations on the timing of delivery are based on gestational age-specific stillbirth risk, and do not formally take into account the benefit gained by reducing neonatal deaths.[11,65] Finally, the risks of fetal death in twins were not assessed beyond 36 weeks gestation, and the rationale behind the choice of the gestational ages for elective delivery is not clear.[7] Other large epidemiological studies on perinatal outcomes in twins were limited by the lack of detail regarding the chorionicity, and the definition of uncomplicated monochorionic pregnancies.[66,67]

Some current recommendations offer expectant management of uncomplicated dichorionic twin pregnancies until 38^{0+6}.[6,8] Based on our findings, this poses a risk of additional 8.8 perinatal deaths compared to delivery a week earlier. Although the estimates for monochorionic pregnancies are not precise, the current policy of delivery at 34^{0+6} weeks as advocated in some guidelines[6,8] has the potential to incur high perinatal deaths. The information on risks provided in twin pregnancies will

complement the ongoing national and international efforts in the to reduce the rates of stillbirths[68] and unexpected neonatal complications in babies born near term.

With a tenth of all twin pregnancies delivering before 32 weeks, our estimates on early preterm neonatal mortality and morbidity provide crucial information to counsel mothers at risk of early preterm delivery.[69-71] Our work has fulfilled the unmet needs in this area, where current estimates on the predicted probability of survival of newborns, especially early preterm twins, are based on extrapolated data from small samples, and do not take into account the effects of chorionicity.[12] Although we did not incorporate economic evaluation in our review, avoiding early delivery has the potential for huge savings to the healthcare system, by up to $70,000 per infant.[60]

The feasibility of a definitive randomised trial on optimal timing of delivery in twin pregnancies is limited, given the huge numbers needed to assess outcomes.[13,14] Individual patient data (IPD) meta-analysis will allow us to assess the effect of factors such as monitoring of the fetuses, level of newborn care, and mode of delivery on outcomes. There is a need to study the effects of delivery before 37 weeks and the loss of a co-twin in monochorionic pregnancies on long-term infant neurodevelopment.[59,72,73]

CONCLUSION

Delivery should be offered to mothers with dichorionic pregnancies at 37 weeks, and considered at 36 weeks in monochorionic twin pregnancies, to minimise the risk of perinatal deaths near term. Our estimates of fetal and neonatal outcomes at various

gestational ages in twin pregnancies should be taken into account while making decisions on timing of delivery.

WHAT IS ALREADY KNOWN

1. Twin pregnancies are at higher risk of stillbirth than singleton pregnancies

2. Stillbirth risk increases with advancing gestational age in uncomplicated monochorionic and dichorionic twin pregnancies

3. The risk of neonatal mortality and morbidity reduces with increasing gestational age in singletons

WHAT THIS STUDY ADDS

1. Women with dichorionic twin pregnancies should be offered delivery at 37 weeks' gestation to prevent significant increase in stillbirths from expectant management compared to neonatal deaths from delivery.

2. In monochorionic twin pregnancies delivery should be considered at 36 weeks' gestation due to the potential increased risks of stillbirths than neonatal deaths.

3. Gestation specific risks of neonatal outcomes in early preterm twin gestations that are provided will aid in the counselling of mothers at risk of early preterm delivery

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DETAILS OF CONTRIBUTORS

Shakila Thangaratinam and Basky Thilaganathan were involved in the conception of the study and the design. Shakila Thangaratinam developed the review protocol. Fiona Cheong-See undertook the search. Fiona Cheong-See and Ewoud Schuit selected the studies, and undertook data extraction. Javier Zamora and David Arroyo-Manzano performed all statistical analyses. Asma Khalil, Jon Barrett, KS Joseph, Elizabeth Asztalos, Karien Hack, Liesbeth Lewi, Arianne Lim, Sophie Liem, Jane E Norman, John Morrison, C Andy Combs, Thomas J Garite, Kimberly Maurel, Vicente Serra, Alfredo Perales, Line Rode, Katharina Worda, Anwar Nassar, Mona Aboulghar, Dwight Rouse, Elizabeth Thom, Fionnuala Breathnach, Francesca M Russo, Julian N Robinson, Jodie Dodd and RBN Soichiro Nakayama contributed to primary study data. Jon Barrett, KS Joseph and Elizabeth Asztalos provided further input into the analysis. Fiona Cheong-See wrote the first draft with input from Shakila Thangaratinam. All authors provided critical input into the manuscript.

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COMPETING INTERESTS

The authors report that there are no conflicts of interest. All authors have completed the Unified Competing Interest form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

TRANSPARENCY DECLARATION

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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FIGURES, TABLES AND APPENDICES

Figure 1   Study selection process in the systematic review on prospective risk of

stillbirth and neonatal complications in uncomplicated twin pregnancies

Figure 2   Quality of studies included in the systematic review on prospective risk

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Appendix 2   Search strategy in Medline for the systematic review on prospective risk

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