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REVIEW ARTICLE

Planned delivery at 37 weeks in twins: a systematic review and meta-analysis of randomized controlled trials

Gabriele Saccone¹ and Vincenzo Berghella²

¹Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy and

²Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA

Abstract

Objective: To evaluate the effects of planned delivery at 37 weeks in women with twin gestations compared to expectant management.

Methods: We performed a systematic review and meta-analysis of randomized controlled trials (RCTs). Searches were performed in electronic databases. We included all RCTs of uncomplicated early term twin gestations with intact membranes who were randomized to planned delivery at 37 weeks or control (i.e. expectant management until at least 38⁰ weeks). The primary outcome was the rate of cesarean delivery.

Results: Two trials (271 women) were analyzed. Women with twin gestations who had planned delivery at 37 weeks had similar rates of cesarean delivery compared to controls [51.9 versus 49.3%; relative risk (RR): 1.05, 95% confidence interval (CI): 0.83–1.32]. Furthermore, no differences in all secondary outcomes were detected, except for a significantly lower rate of serious adverse infant outcomes in the women who had planned delivery at 37 weeks compared to controls (4.7 versus 12.2%; RR: 0.39, 95% CI: 0.20–0.76).

Conclusions: Planned delivery at 37 weeks in twins is associated with a similar risk of cesarean delivery and lower risk of serious adverse infant outcomes, compared to expectant management until at least 38 weeks.

Keywords

Cesarean, death stillbirth, elective, multiple gestations, neonatal, perinatal, pregnancy

History

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Introduction

The incidence of twin gestations in USA has increased over the past decades [1]. Although twin pregnancies have an increased risk of preterm birth (PTB), ~46% will give birth after 37 weeks of gestation [2]. For women whose twin pregnancy continues beyond 37 weeks of gestation, there is a higher risk of perinatal mortality and morbidity [3]. Multiple population-based studies consistently indicate that the lowest risk of perinatal mortality and morbidity for twins occurs with births between 36 and 38 weeks [4]. However, the risk of maternal and perinatal complications with induction at 37 or 38 weeks for twins is still a subject of debate [5–7]. While a prior meta-analysis has been published, data on several outcomes from the included trials was not available [5], prompting an attempt at a more complete analysis.

The aim of this study was to evaluate the effect of a policy of planned delivery at 37 weeks compared to expectant management in women with asymptomatic and uncomplicated twin gestations.

Methods

Searches were performed in electronic databases (Scopus, EMBASE, MEDLINE, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, ClinicalTrials.gov, OVID and the Cochrane Central Register of Controlled Trials) using these words: “induction”, “cesarean section”, “expectant management”, “twins” and “pregnancy” from inception of each database to November 2014 with no restrictions for language.

We included all randomized controlled trials (RCTs) of asymptomatic and uncomplicated twin gestations at 37⁰–37⁶ weeks with intact membranes who were randomized to planned delivery or control (i.e. expectant management until at least 38⁰ weeks). All published RCTs on induction of labor at term were carefully reviewed. Only trials on asymptomatic dichorionic/diamniotic, or monochorionic/diamniotic twin gestations without premature rupture of membranes (PROM) were included. Exclusion criteria included quasi-randomized trials, trials in women with PROM, trials in women with high risk pregnancy (i.e. intrauterine growth restriction, diabetes in pregnancy, gestational hypertension/preeclampsia, oligohydramnios, fetal macrosomia), trials including monochorionic/monoamniotic twins and trials in women with singleton gestations.

Address for correspondence: Dr Vincenzo Berghella, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Thomas Jefferson University, 833 Chestnut Street, First Floor, Philadelphia, PA 19107, USA. Tel: +1-215-955-7996. Fax: +1-215-503-6619. E-mail: vincenzo.berghella@jefferson.edu

The risk of bias in each included study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [8]. Data abstraction was completed by two independent investigators (G.S. and V.B.). Each investigator independently abstracted data from each study and analyzed data separately. The primary outcome selected was the rate of cesarean delivery. Secondary outcomes included spontaneous vaginal delivery (SVD), operative vaginal delivery (forceps or vacuum), chorioamnionitis, postpartum blood loss, rate of hysterectomy and neonatal outcomes including meconium-stained amniotic fluid (MSAF), PROM, APGAR score <7 at 5 min, birth weight, admission to neonatal intensive care unit (NICU), perinatal death and serious adverse infant outcome (as defined by authors). All authors were contacted for missing data. We planned a subgroup analysis according with the chorionicity. Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration no.: CRD42014014133).

The data analysis was completed independently by authors (G.A. and V.B.) using Review Manager 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). The completed analyses were then compared, and any difference was resolved by consensus. Statistical heterogeneity between studies was assessed using Higgins I^2 statistics. In case of statistically significant heterogeneity ($I^2 > 50\%$) the random effects model was used, otherwise a fixed effect model was planned. The summary measures were reported as relative risk (RR) with 95% confidence interval (95% CI). p value <0.05 was considered statistically significant. The meta-analysis was performed following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [9].

Results

We initially identified 16 RCTs evaluating the efficacy of planned delivery at 37 weeks [6,7,10–23]. Fourteen RCTs were excluded because they were on singleton gestations [10–23]. Two studies which met inclusion criteria for this meta-analysis were analyzed [6,7]. Figure 1 shows the flow diagram (PRISMA template) of information through the different phases of the review.

Both of the studies had a low risk of bias according with the Cochrane Collaboration's tools. No study was double blind because this was deemed difficult methodologically given the intervention (Figure 2).

The characteristics of the two included trials are summarized in Table 1. Of the 271 women, 133 (49%) were randomized to delivery group, while 138 (51%) to control one. Eighty percent were dichorionic/diamniotic twin gestations. The heterogeneity between the studies was low ($I^2 < 50\%$) and so a fixed effect model was used to obtain the pooled RR. Funnel plot shows no publication bias (Figure 3).

Women with twin gestations who had planned delivery at 37 weeks had a similar rate of cesarean delivery compared to controls (51.9% versus 49.3%; RR: 1.05, 95% CI: 0.83–1.32) (Table 2, Figure 4). Furthermore, we found no differences in all secondary outcomes, except for the rate of serious adverse infant outcomes (as defined by the authors of the included

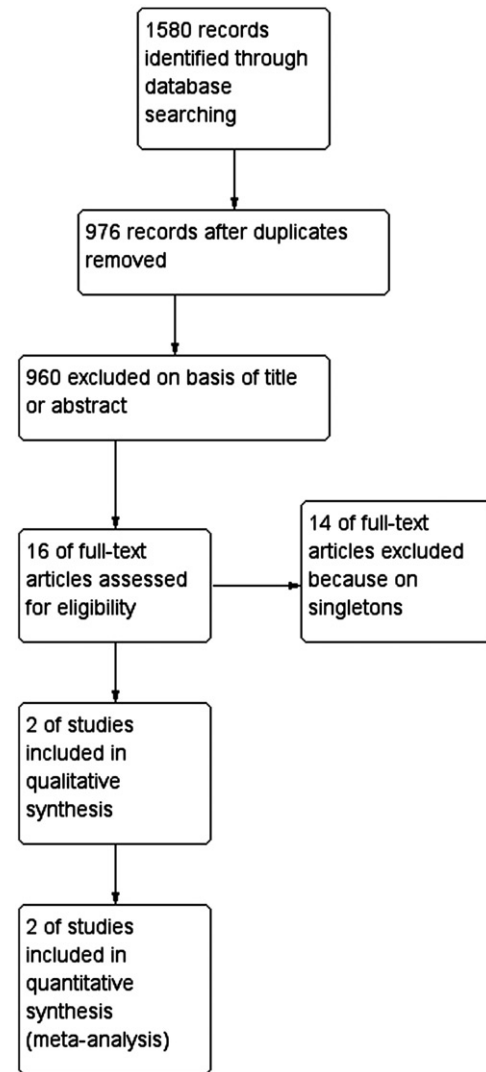


Figure 1. Flow diagram of studies identified in the systematic review (PRISMA template).

studies) which was lower in the women who had planned delivery at 37 weeks compared to controls (4.7% versus 12.2%; RR: 0.39, 95% CI: 0.20–0.76) (Table 2, Figure 5). Serious adverse infant outcome was defined by the primary trial as perinatal death or serious neonatal morbidity defined as one or more of the following: birth trauma (subdural or intracerebral hemorrhage, spinal cord injury, basal skull fracture, other fracture or peripheral nerve injury present at discharge from hospital); birth weight less than third centile for gestational age at birth and infant sex; APGAR score <4 at 5 min; cord pH <7.0 (arterial or venous cord blood); seizure at <24 h of age or requiring two or more drugs to control; neonatal encephalopathy Grade 3 or 4; use of ventilation >24 h, admission to NICU >4 days; severe respiratory distress syndrome; chronic lung disease; proven necrotizing enterocolitis; proven systemic infection within 48 h of birth treated with antibiotics) [7]. Data about chorioamnionitis were not available. Neither study stratified data by chorionicity.

Discussion

This meta-analysis of pooled data of the two RCTs evaluating the effect of a policy of planned delivery at 37 weeks in women with asymptomatic and uncomplicated twin gestations

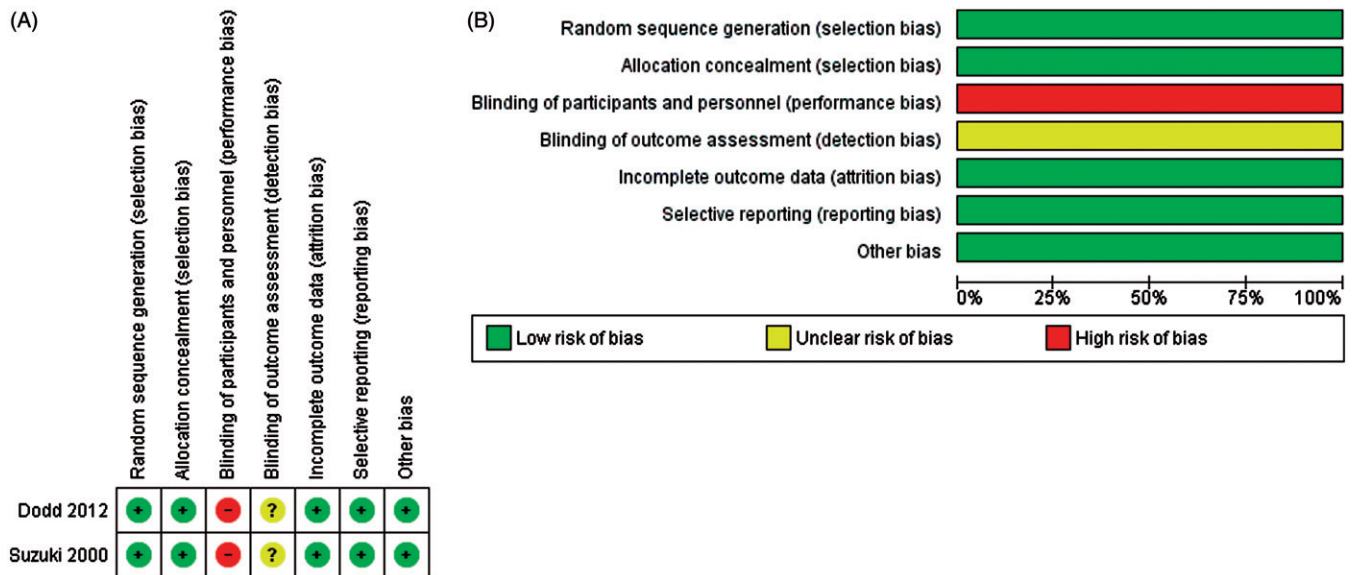


Figure 2. Assessment of risk of bias. (A) Summary of risk of bias for each trial; plus sign, low risk of bias; minus sign, high risk of bias; question mark, unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

Table 1. Characteristics of the included studies.

| Characteristics | Suzuki et al. [6] | Dodd et al. [7] |
|--|--|---|
| Location | Japan | Australia |
| Sample size, <i>n</i> (planned delivery/control) | 36 (17 versus 19) | 235 (116 versus 119) |
| Inclusion criteria | Uncomplicated twins, first twin in cephalic presentation | Uncomplicated twins |
| Induction method | PGE ₂ 0.5 mg orally, oxytocin | Not reported |
| Control group | Expectant management until spontaneous labor | Expectant management until spontaneous labor or induction if required |
| Dichorionic/diamniotic | 22 (11 versus 11) | 193 (98 versus 95) |
| Monochorionic/diamniotic | 14 (6 versus 8) | 40 (19 versus 21) |
| GA at randomization (weeks ^{days}) | 37 ⁰ –37 ⁶ | 37 ⁰ –37 ⁶ |
| Study primary outcome | Rate of cesarean delivery | Serious adverse infant outcome |

Data are presented as total number (*n* intervention versus control). GA, gestational age; PGE₂, prostaglandin E₂.

shows that planned delivery at 37 weeks is associated with a similar risk of cesarean delivery compared to expectant management until 38 weeks or more. Furthermore, planned delivery at 37 weeks is associated with a significantly 61% lower risk of serious adverse infant outcome in these twin gestations.

One prior meta-analysis evaluated this issue of planned birth at 37 weeks in twins [5]. This study included the same two trials as ours, but did not have extra unpublished data (i.e. spontaneous and operative vaginal delivery, NICU admission, hysterectomy and birth weight) which were kindly obtained from the authors of one trials [6]. Furthermore, the Cochrane Review did not report data about serious adverse infant outcome, which was statistically significant in our meta-analysis [5]. These additional data made possible the cumulative reporting from both trials on most outcomes.

One of the strengths of our study is the inclusion of RCT data on induction of pregnancy in a specific population, i.e. asymptomatic and uncomplicated twins. Furthermore, both the included studies had a low risk of bias according with the Cochrane Collaboration's tools. We also were able to obtain unpublished data from one of the trials [6].

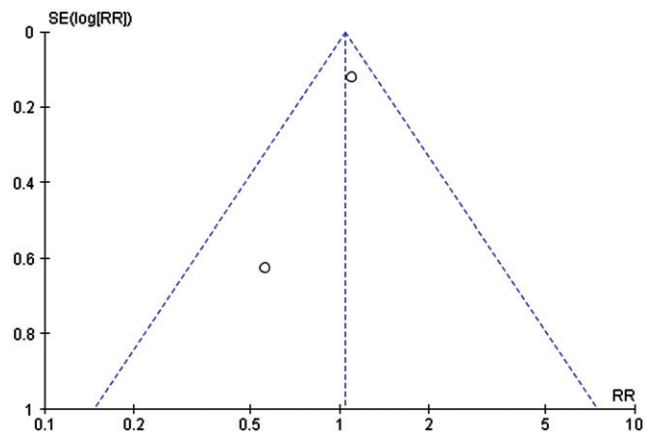


Figure 3. Funnel plot for assessing publication bias.

Limitations of our study are those inherent to any other meta-analysis. Other shortcomings of our meta-analysis are the relatively limited numbers of trials ($n=2$) and twins included ($n=271$). This small sample size may have made it difficult to identify key differences in some of the secondary

Table 2. Primary and secondary outcomes of the included studies.

| Outcomes | Suzuki et al. [6] | Dodd et al. [7] | Total | RR (95% CI) |
|--|--|-----------------|--------------------------------------|--|
| Cesarean delivery | 3 versus 6 | 66 versus 62 | 69/133 (51.9%) versus 68/138 (49.3%) | 1.05 (0.83–1.32) |
| Cesarean delivery for non-reassuring fetal testing | 0 versus 1 | 6 versus 7 | 6/133 (4.5%) versus 8/138 (5.8%) | 0.79 (0.29–2.15) |
| SVD | 10 versus 9 | 34 versus 31 | 44/133 (30.1%) versus 40/138 (29.0%) | 1.59 (0.42–5.95) |
| Operative vaginal delivery | First twin: 0 versus 1 second twin 4 versus 4 | 16/versus 6 | 20/266 (7.5%) versus 31/276 (11.3%) | 0.67 (0.39–1.15) |
| Blood loss (mean, in mL) | 571 versus 577 | N/A | – | Mean difference –6.00 mL (95% CI –237.95 to 229.95) |
| Blood transfusion | 0 versus 1 | 2 versus 4 | 2/133 (1.5%) versus 5/138 (3.6%) | 0.48 (0.11–2.08) |
| Maternal death or serious morbidity | N/A | 2 versus 7 | 2/116 (1.7%) versus 7/116 (6.0%) | 0.29 (0.06–1.38) |
| Hysterectomy | 0 versus 0 | N/A | 0/17 (0%) versus 0/19 (0%) | N/E |
| Meconium stained | 0 versus 5 | 7 versus 5 | 7/266 (2.6%) versus 10/276 (3.6%) | 0.52 (0.04–7.35) |
| PROM | 0 versus 7 | N/A | 0/17 (0%) versus 7/19 (36.8%) | 0.07 (0.00–1.21) |
| APGAR <7 at 5 min | 0 versus 0 | 0 versus 3 | 0/266 (0%) versus 3/276 (1.1%) | 0.15 (0.01–2.82) |
| Birth weight first twin | 2771 versus 2690 | N/A | – | Mean difference 81.00 g (95% CI –152.63 to 314.63) |
| Birth weight second twin | 2629 versus 2654 | N/A | – | Mean difference –25.00 g (95% CI –172.37 to 122.37) |
| Birth weight <2500 g | 11 versus 13 | 55 versus 41 | 66/266 (24.8%) versus 54/276 (19.6%) | 1.28 (0.93–1.75) |
| NICU | 0 versus 0 | 7 versus 7 | 7/266 (2.6%) versus 7/276 (2.5%) | 1.01 (0.35–2.46) |
| Perinatal death | 0 versus 0 | 0 versus 1 | 0/249 (0%) versus 1/254 (0.4%) | 0.34 (0.01–8.25) |
| Serious adverse infant outcome* | N/A | 11 versus 29 | 11/232 (4.7%) versus 29/238 (12.2%) | 0.39 (0.20–0.76) |

Data are presented as *n* intervention versus *n* control. SD, standard deviation; N/A, not available; birth weight, mean in grams. *Serious adverse infant outcome: perinatal death or serious neonatal morbidity defined as one or more of the following: birth trauma (subdural or intracerebral hemorrhage, spinal cord injury, basal skull fracture, other fracture or peripheral nerve injury present at discharge from hospital); birth weight less than third centile for gestational age at birth and infant sex; APGAR score <4 at 5 min; cord pH <7.0 (arterial or venous cord blood); seizure at <24 h of age or requiring two or more drugs to control; neonatal encephalopathy Grade 3 or 4; use of ventilation >24 h, admission to NICU >4 days; severe respiratory distress syndrome; chronic lung disease; proven necrotizing enterocolitis; proven systemic infection within 48 h of birth treated with antibiotics).

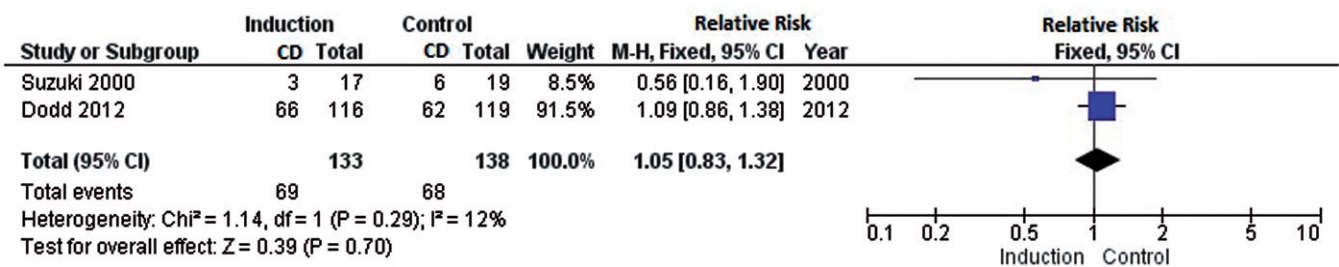


Figure 4. Forest plot for cesarean delivery. CD, cesarean delivery.

outcomes. About 85% of the patients in our meta-analysis are from one trial, which was of high quality [7]. The most important limitation is that neither study stratified data by placental chorionicity, which is recognized as a leading risk factor for stillbirth [24]. Indeed, monochorionic twins have a higher risk of stillbirth compared with dichorionic twins [24].

We conclude that, as planned delivery at 37 weeks in twins is associated with similar risks of cesarean delivery and lower risks of serious adverse infant outcome, serious consideration should be given to adopt a policy of planned delivery for all asymptomatic and uncomplicated twin gestations at 37 weeks. These results are particularly applicable to

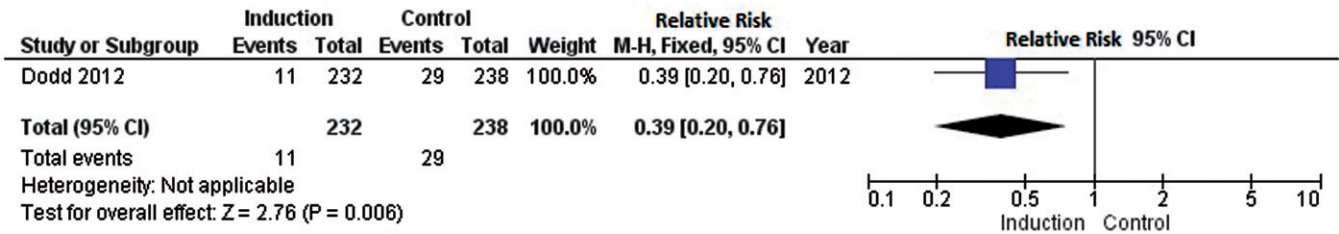


Figure 5. Forest plot for serious adverse infant outcome.

dichorionic/diamniotic twins, which comprised 80% of the women included. They do apply to all women with uncomplicated twin gestations, either planning to deliver by induction [6,7], or by cesarean delivery, if so indicated [7].

Based on these Level 1 data, planned delivery at 37 weeks in uncomplicated twins is associated with no increased risk of cesarean delivery and with lower serious adverse infant outcomes compared to expectant management until at least 38 weeks.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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