
OBSTETRICS

Factors Associated with Neonatal Morbidity or Early Neonatal Mortality in Twin Pregnancies at Chonburi Hospital

Wirada Dulyaphat, MD*,
Teerapat Chullapram, MD*.

* Department of Obstetrics and Gynecology, Chonburi Hospital, Chonburi 20000, Thailand

ABSTRACT

Objective: To determine the factors contributing to neonatal morbidity and/or early neonatal mortality in twin pregnancies.

Materials and Methods: A case-control study was performed by 220 twin pregnant women who delivered at 28 weeks of gestation or beyond at Chonburi Hospital from March 2012 to January 2014. Cases were 55 twin pregnancies with unfavorable outcomes on both neonates, including neonatal morbidity and/or early neonatal mortality, while controls were 165 twin pregnancies with favorable outcomes on both neonates. Antepartum and intrapartum characteristics were compared between both groups. The associated factors were determined by univariate and multivariate logistic regression model.

Results: Complete data from chart reviewed of 220 twin pregnancies were obtained. These factors including preterm birth before 34 weeks, monochorionicity, premature rupture of membranes (PROM), PROM beyond 18 hours, being referred cases, birth weight discordancy greater than 25% and Apgar score less than or equal to 7 at 1 and 5 minutes were significantly associated to adverse neonatal outcomes ($p < 0.05$). By the multivariate analysis, preterm birth before 34 weeks and birth weight discordancy more than 25% remained statistically significant (OR 5.65, 95% CI 1.1-3.4, $p < 0.001$ and OR 3.12, 95% CI 2.6-5.7, $p < 0.001$, respectively). No statistically significant difference between 2 groups in maternal complication including pregnancy induced hypertension (PIH), postpartum hemorrhage (PPH) and puerperal infection (urinary tract infection (UTI), wound infection).

Conclusion: Preterm birth before 34 weeks and birth weight discordancy more than 25% were associated with neonatal morbidity and/or early neonatal mortality in twin pregnancies.

Keywords: Risk factors, neonatal morbidity, early neonatal mortality, twin pregnancies

Correspondence to: Teerapat Chullapram, MD., Department of Obstetrics & Gynecology, Chonburi hospital Chonburi 20000, Thailand.
Tel: 66-3-8931331, Fax: 66-3-8931331, Email address: j_harmonica@hotmail.com, tchullapram@gmail.com

Introduction

Because of advanced maternal age and tend to

use of assisted reproductive techniques, the incidence of twin pregnancy was significantly increased worldwide

within the past 20 years, accounted for approximately 2 to 4% of all births⁽¹⁻³⁾. Twin pregnancies not only increased maternal but also fetal and neonatal morbidity and mortality^(4,5). The incidence of pregnancy induced hypertension (PIH), postpartum hemorrhage (PPH), peripartum hysterectomy and maternal death were significantly increased by two folds or more in twin pregnancy compared with singleton^(6,7). Steenhaut P et al⁽²⁾ and Cunningham FG et al⁽⁴⁾ found that twin pregnancies also came with higher incidence of adverse neonatal outcome, primarily due to increase of preterm birth rate. In addition, Glinianaia SV et al⁽⁸⁾ showed that twin pregnancies were also associated with higher incidence of premature separation of placenta, umbilical cord prolapse and neonatal mortality rate.

Several factors have been proposed as risk for unfavorable neonatal outcome. Gezer A et al⁽⁹⁾ found that perinatal mortality and morbidity rates were higher in monozygosity twin. The author also observed that prematurity was the principal cause of perinatal mortality. From studies of Corinna P et al in Germany⁽¹⁰⁾ and Tobe RG et al in Japan⁽¹¹⁾, birth weight discordancy more than 25% tend to be a pathologic process and related to unfavorable neonatal outcome.

From existing literatures, most of these studies were conducted using singleton pregnancies as the controlled group, or conducted on the basis of single suspected risk factor. Nor did the comparison were made between corresponding twin pregnancies groups. As mention, we aimed to determine the factors associated with unfavorable outcome in twins by compare with twin pregnancy with favorable outcomes. Hopefully, the result of this study might somehow provide some data which may help improving the evaluation of twin pregnancies and prevent the undesirable outcome in the future.

Materials and Methods

A retrospective case control study was approved by Institutional Review Board of Chonburi Hospital, Thailand. All twin pregnant women who delivered at Chonburi Hospital during March 2012 to January 2014 were reviewed from the hospital database. Inclusion criteria were all twin pregnant women who delivered at

28 weeks of gestation or beyond and/or birth weight of both neonates more than 1,000 grams with corresponding neonatal outcome defined in the section below. Exclusion criteria were known case of dead fetus in utero (DFIU) and/or fetal anomaly of one or both fetuses, no document of chorionicity and/or amnioticity and incomplete patients' data. The medical records of both maternal and neonatal data were obtained.

Sample size was estimated based on a previous study⁽¹⁰⁾, which indicate that the probability of exposure to birth weight discordancy more than 25% among control group (defined as cases without admission to neonatal intensive care unit) is 2.7%. The true odd ratio for disease in exposed subjects relative to unexposed subjects is 6.12. With a level of statistical significance of 0.05% (α -error = 0.05) and a power of study of 80% (β -error = 0.2), we obtained a sample size in a set of twin of 54 subjects per group after addition of 10% of calculated subjects.

The study population was divided into two groups: case and control groups. Cases referred to twin pregnancies with unfavorable outcomes including neonatal morbidity and/or early neonatal mortality, while controls referred to pregnancies with favorable outcomes. The assigned case-to-control ratio was 1:3. When one case subject was selected, three control subjects would then be chosen from three women who gave birth at the closest time to delivery of each case. In our study, the definition of unfavorable neonatal outcome group consist of early neonatal mortality with or without neonatal morbidity. Early neonatal mortality defined as the death of live birth during the first 7 days after birth⁽⁴⁾. Neonatal morbidity defined by having at least one of the following conditions from the neonatal medical records including, 1. Use of ventilation or nasal continuous positive airflow pressure (nCPAP). 2. Any infection or sepsis occurred during the first 7 days after birth 3. Present of interventricular hemorrhage (IVH) grade 3, 4 by Papile classification 4. Record of admission to neonatal intensive care unit (NICU). Corresponding neonatal outcome defined as twin neonates with or without early neonatal mortality and morbidity on both neonates.

The primary outcome was factors which

associated with unfavorable neonatal outcome. Secondary outcomes were incidence of maternal complications and maternal death.

Statistical analysis

Data were analyzed with SPSS version 17 (SPSS Inc, Chicago, IL, USA). Continuous variables were presented as mean with standard deviation and categorical variables as number with percentage. T-test or Mann-Whitney U test were used to compare difference of continuous data depending on their distribution. Fisher’s exact or chi-square test were used to compare continuous data. Logistic regression analysis was performed to identify independent factors

associated with unfavorable outcome. Statistically significant differences were defined as $p < 0.05$.

Result

During the study period, 262 twin pregnancies were assessed for eligibility. Forty two subjects were excluded due to incomplete data or diagnosed with DFIU or fetal anomaly. The remaining two hundred and twenty subjects were included in the study. Fifty five twin pregnancies were categorized into unfavourable outcome group. The remaining 165 twin pregnancies were categorized into favourable outcome group. A participant flow diagram is shown as Fig. 1.

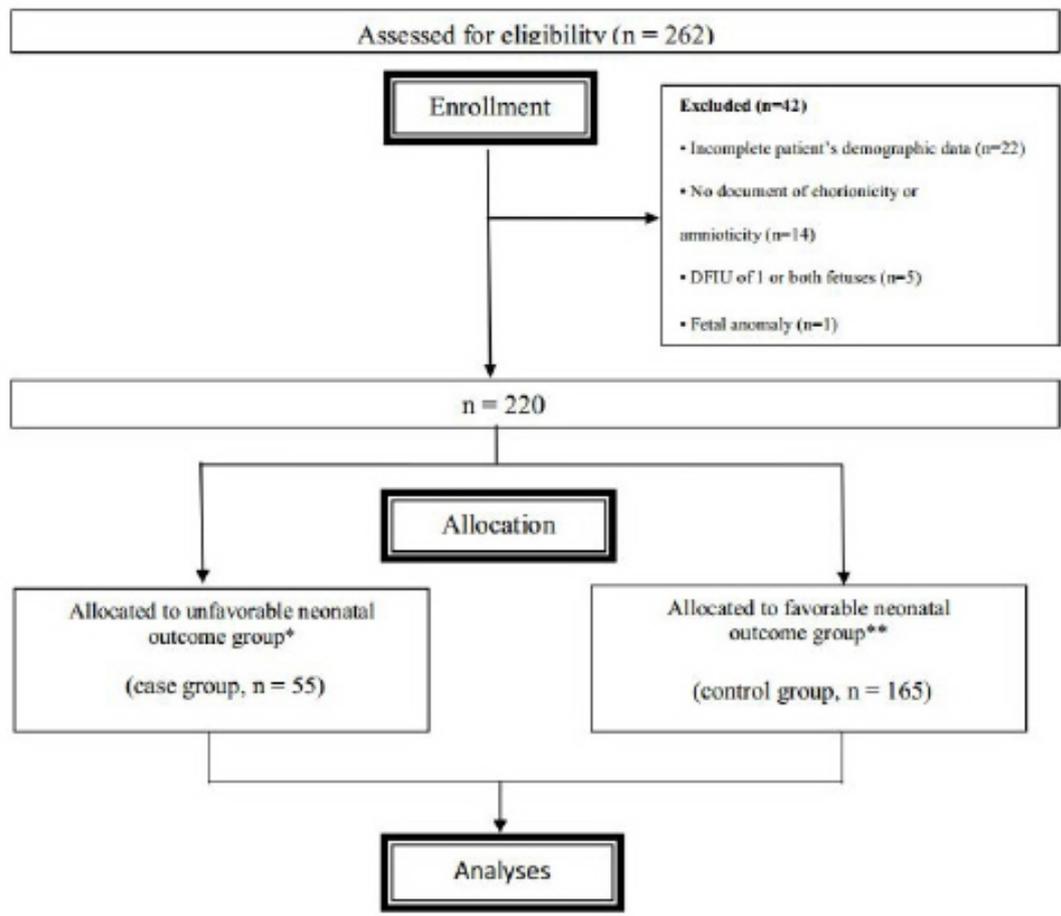


Fig. 1. Flow of the population of the study
 * Unfavorable neonatal outcome group: consist of early neonatal mortality with or without neonatal morbidity on both twin.
 ** Favorable neonatal outcome group: no early neonatal mortality and neonatal morbidity on both twin.

There was no significant difference between groups in maternal demographic data (Table 1). We found that the unfavorable neonatal outcome group (case group) had significantly higher rates of preterm birth before 34 weeks, monochorionicity, PROM, PROM beyond 18 hours and referral cases than the favorable neonatal outcome group (control group). The mean gestational age (GA) at delivery of case and control subjects were 31.5 ± 2.2 weeks and 35.7 ± 2.3 weeks respectively. There was no significant difference

between groups in other maternal clinical characteristics. With respect to their neonatal demographic data (Table 2), there were significantly higher rates of birth weight discordancy more than 25% and low Apgar score at 1 and 5 minutes (defined by Apgar score ≤ 7 according to world health organization (WHO), the International Classification of Disease (ICD) 10) in unfavorable neonatal outcome group (case group). The mean Apgar score of case and control subjects at 1 and 5 minutes were 6 ± 2 , 8 ± 2 and 7 ± 2 , 9 ± 2 respectively.

Table 1. Maternal demographic data and clinical characteristics.

| | Unfavorable neonatal outcome group (N=55) | Favorable neonatal outcome group (N=165) | P |
|--|---|--|---------|
| Maternal parameters : demographic data | | | |
| Maternal age < 20 years | 8 (14.5) | 22 (13.3) | 0.224 |
| Maternal age > 35 years | 12 (21.8) | 40 (24.2) | 0.379 |
| Maternal age (years) | 30.6 (8.8) | 31.1 (7.6) | 0.250 |
| Education | | | |
| Bachelor degree or higher | 13 (23.7) | 47 (28.5) | 0.671 |
| Lower than Bachelor | 42 (76.3) | 118 (71.5) | |
| Occupation | | | |
| Civil servant | 6 (11.4) | 20 (12.9) | 0.568 |
| Housewife | 13 (23.6) | 40 (24.2) | |
| Others | 36 (65.0) | 105 (62.9) | |
| Nationality | | | |
| Thai | 35 (63.6) | 102 (61.9) | 0.342 |
| Non-Thai | 20 (36.4) | 63 (38.1) | |
| Maternal parameters: clinical characteristics | | | |
| GA at delivery < 34 weeks | 32 (58.1) | 41 (24.8) | < 0.001 |
| Monochorionicity | 24 (43.6) | 38 (23.0) | < 0.001 |
| Artificial fertilization | 1 (1.5) | 2 (1.2) | 0.841 |
| Chronic hypertension | 4 (7.2) | 19 (11.5) | 0.064 |
| GDM | 9 (16.3) | 29 (17.5) | 0.351 |
| Cesarean section | 42 (76.3) | 114 (69.1) | 0.711 |
| PROM | 25 (45.4) | 50 (30.3) | 0.028 |
| PROM > 18 hours | 7 (12.7) | 10 (6.0) | 0.045 |
| Referral case | 24 (43.6) | 44 (26.6) | 0.032 |

Data were presented in n (%) or Mean (SD), Abbreviation; GDM = gestational diabetes mellitus; PROM = premature rupture of membrane, * Chi-square test

Table 2. Neonatal demographic data.

| | Unfavorable neonatal outcome group (N=55) | Favorable neonatal outcome group (N=165) | P |
|--|---|--|--------|
| Neonatal parameters | | | |
| BW discordancy > 25% | 3(5.4) | 5(3.0) | 0.025 |
| Low Apgar score 1 minute (≤ 7) | 30(54.5) | 24(14.5) | <0.001 |
| Low Apgar score 5 minutes (≤ 7) | 11(21.8) | 7(4.2) | <0.001 |

Data were presented in n (%), Abbreviation; BW = birth weight, * Chi-square test

Since we found that eight maternal and neonatal demographic characteristics including preterm birth before 34 weeks, monochorionicity, PROM, PROM beyond 18 hours, referral cases, birth weight discordancy more than 25% and low Apgar score at 1 and 5 minutes of both twin neonates were significantly different between the two groups, we then performed further analysis to determine whether these variables were independent risk factors for early neonatal mortality or

neonatal morbidity on both twin.

When multivariable analysis with adjustment for potential confounding factors was performed (Table 3), two variables were identified as independent risk factors. These included preterm birth before gestational age of 34 weeks (OR 5.65, 95% CI = 1.1 - 3.4) and birth weight discordancy more than 25% (OR 3.12, 95% CI = 2.6 - 5.7).

Table 3. Multivariate logistic regression analysis; contributing factors associated to unfavorable neonatal outcome.

| | Adjusted OR | 95% CI | P |
|------------------------------|-------------|---------|---------|
| Maternal parameters | | | |
| GA < 34 weeks | 5.65 | 1.1-3.4 | < 0.001 |
| Monochorionicity | 2.01 | 0.1-1.4 | 0.836 |
| PROM | 2.24 | 0.4-6.2 | 0.652 |
| PROM > 18 hours | 1.35 | 0.2-4.8 | 1.128 |
| Referral case | 0.62 | 0.6-7.5 | 0.732 |
| Neonatal parameters | | | |
| BW discordancy > 25% | 3.12 | 2.6-5.7 | < 0.001 |
| Low apgar score at 1 minute | 2.16 | 0.8-4.2 | 1.071 |
| Low apgar score at 5 minutes | 1.08 | 0.4-6.3 | 0.105 |

Abbreviation; PROM = GA = gestational age; premature rupture of membrane; BW = birth weight

Table 4 showed maternal complication between 2 groups. There were no significant differences in maternal complication between 2 groups including pregnancy induced hypertension (PIH), postpartum

hemorrhage (PPH) and puerperal infection (urinary tract infection (UTI), wound infection) rate. There is no peripartum hysterectomy or maternal death in this study.

Table 4. Maternal complication and clinical characteristics.

| | Unfavorable neonatal outcome group (N=55) | Favorable neonatal outcome group (N=165) | P * |
|---------------------|---|--|-------|
| PIH | 12(21.8) | 41(24.8) | 0.103 |
| PPH | 2(3.6) | 5(3.0) | 0.083 |
| Puerperal infection | 3(5.4) | 7(4.2) | 0.251 |
| UTI | 2 | 5 | |
| Wound infection | 1 | 2 | |

Data were presented in n (%), Abbreviation: PIH = pregnancy induced hypertension; PPH = postpartum hemorrhage; UTI = urinary tract infection, *Chi-square test

Discussion

Compared with singleton, twin pregnancies increase the risk of adverse outcome to both mother and her neonates^(4, 5). Our study concentrated on finding the factors which may contribute to unfavourable outcome in neonates. We defined the unfavourable outcome as the present of neonatal mortality or morbidity. While there is a standard definition of neonatal mortality. Neonatal morbidity, on the other hand, has not been clearly defined. We decided to use the definition of neonatal morbidity from previous study⁽¹⁰⁾.

With the definition of unfavourable neonatal outcome discussed previously. We found two out of 18 risk factors were independently associated with unfavorable neonatal outcomes including preterm birth before gestational age of 34 weeks and discordancy of birth weight more than 25%.

These findings are congruent with Corinna P, et al⁽¹⁰⁾, Steenhaut P, et al⁽²⁾ and Cunningham FG, et al⁽⁴⁾, shown that prematurity and birth weight discordant more than 25% were significantly associated with higher perinatal morbidity and adverse early neonatal outcome. Twin pregnancies also came with higher incidence of preterm birth rate, which correspondingly compromised neonatal survival rate and increased the risk of lifelong disability. With a discordancy of more than 25%, there is an increased risk of caesarean section delivery for non-reassuring fetal heart rate tracing, neonatal acidosis, admission to NICU, and respiratory distress syndrome^(11,12).

Premature rupture of membrane (PROM) or premature rupture of membrane beyond 18 hours are also not related to neonatal morbidity in our study displaying the same result as in previous studies⁽¹³⁾ which suggested that rupture of membranes per se did not cause any deleterious clinical manifestations or poor neonatal outcome and encouraged the conservative management of twin pregnancies with PPRM.

Contrary to our result, Glinianaia SV, et al⁽⁸⁾ and Kea H, et al⁽¹⁴⁾, found that monochorionicity was significantly associated with neonatal mortality and neuro morbidity, but our study was conducted base on logistic regression analysis.

With the high incidence of referral case in Chonburi province, Thailand. We decided to include the referral cases as study parameter. Our study did not find any correlation to unfavorable neonatal outcome for this factor.

Previous studies^(15,16) suggested that pregnancies complicated by placenta previa or placental abruption were associated with higher risk of neonatal mortality and lower neonatal birth weight in both of singletons and multiples pregnancy. Our study found only one set of twin pregnancy with placenta previa, and was safely delivered without antepartum or intrapartum bleeding. Although both neonates had favorable outcome, they may not be a good representation of result due to low number of case. There was no documentation of placental abruption in this study.

The incidence of maternal complications between twin pregnancies and singleton at Chonburi

hospital in this study was comparable to the result in previous study⁽¹⁷⁾ conducted in Ramathibodi Hospital posting the higher incidence of complications by 3 times in twin pregnancies.

The strength of our study is that the comparison were made between twin neonates which were born with the same neonatal outcome. This could eliminate the confounding factors and help strengthen the validity of result. Our study also summarized all risk factors mentioned in previous studies and conduct multivariate analysis to identify significant factors.

The limitation of our study was retrospective design, and the data was gathered from inpatients' chart data. It is possible that some antenatal diagnosis by ultrasound were over-diagnosed or under-diagnosed, which might interfere the result interpretation.

At present, both significant factors are considered as non-modifiable risk factors. However, a recently published, multicenter, open-randomized controlled trial conducted by Goya MM, et al⁽¹⁸⁾ found that placement of a vaginal pessary in twin pregnancy with short cervical length (≤ 25 mm) measured at 23 weeks leads to a reduction in the incidence of spontaneous delivery before 34 completed weeks compared with expectant management without serious adverse effects associated with the use of a cervical pessary.

In the near future, if we are able to prolong the gestational age to surpass 34 weeks, or reduce the discordancy of birth weight by mean of early detection. We might be able to improve the neonatal outcome in twin pregnancies. However, further large scale multicenter study might be required to confirm the result of this study.

Conclusion

Preterm birth with gestational age less than 34 weeks and birth weight discordancy more than 25% were associated with neonatal morbidity and/or early neonatal mortality in twin pregnancies. There were no significant differences in maternal complications. There is no peripartum hysterectomy or maternal death in this study.

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ปัจจัยที่สัมพันธ์ต่ออัตราทุพพลภาพหรืออัตราตายทารกแรกคลอดครรภ์แฝดที่มาคลอดที่โรงพยาบาลชลบุรี

วิรดา ดุลยพัชร์, อธิภัทร์ จุลละพราหมณ์

วัตถุประสงค์: เพื่อศึกษาปัจจัยที่เกี่ยวข้องต่ออัตราทุพพลภาพ และ/หรือ อัตราตายทารกแรกคลอดในทารกครรภ์แฝด

วิธีการวิจัย: ศึกษาด้วยวิธีเคส-คอนโทรลในทารกครรภ์แฝดอายุครรภ์ตั้งแต่ 28 สัปดาห์ ที่มาคลอดที่โรงพยาบาลชลบุรีตั้งแต่เดือนมีนาคม 2555 ถึง มกราคม 2557 ปัจจัยเสี่ยง 18 ปัจจัย ถูกวิเคราะห์หาความสัมพันธ์แบบตัวแปรเดียวและพหุตัวแปร

ผลการวิจัย: ในหญิงตั้งครรภ์แฝด 220 คน แบ่งกลุ่มการศึกษาเป็น 2 กลุ่มคือ กลุ่มทารกที่ไม่พึงปรารถนาทั้งคู่ (unfavorable outcome group) เป็นกลุ่มศึกษา และกลุ่มทารกที่พึงปรารถนาทั้งคู่ (favorable outcome group) เป็นกลุ่มควบคุม หลังวิเคราะห์ความสัมพันธ์พหุตัวแปรพบว่า การคลอดก่อนกำหนดที่อายุครรภ์น้อยกว่า 34 สัปดาห์ น้ำหนักทารกแฝดทั้งคู่แตกต่างกันมากกว่า 25% (bodyweight discordancy) มีความสัมพันธ์ต่ออัตราทุพพลภาพและ/หรืออัตราตายทารกแรกคลอดครรภ์แฝดอย่างมีนัยสำคัญทางสถิติ (Adjusted OR : 5.65, $p < 0.001$) และ (Adjusted OR : 3.12, $p < 0.001$) ตามลำดับ ภาวะแทรกซ้อนในมารดาทั้ง 2 กลุ่ม ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ ไม่มีอุบัติการณ์ดัดมดลูกหลังคลอด หรือ มารดาเสียชีวิตในงานวิจัยนี้

สรุป: การคลอดก่อนกำหนดที่อายุครรภ์น้อยกว่า 34 สัปดาห์ และ/หรือ การมีน้ำหนักทารกแตกต่างกันมากกว่า 25% (bodyweight discordancy) มีความสัมพันธ์ต่ออัตราทุพพลภาพ และ/หรือ อัตราตายทารกแรกคลอดครรภ์แฝดอย่างมีนัยสำคัญทางสถิติ