A RETROSPECTIVE STUDY (2009- 2018) ON THE OUTCOME OF UNCOMPLICATED TWIN PREGNANCIES IN HOSPITAL SULTAN ISMAIL JOHOR BAHRU: THE ASSOCIATION BETWEEN GESTATIONAL AGE AT DELIVERY AND THE NEONATAL OUTCOMES

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Dissertation Submitted in Partial Fulfilment of the Requirement for the Degree of Master of Medicine (Obstetrics and Gynaecology)

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ABBREVIATIONS

ART	assisted reproductive technique
AS	Apgar score
CS	caesarean section
DCDA	dichorionic diamniotic
GA	gestational age
IUGR	intrauterine growth restriction
IUI	Intrauterine insemination
IVF	in vitro fertilization
LBW	low birth weight
MCDA	monochorionic diamniotic
MOD	mode of delivery
MRN	medical registration number
NICU	neonatal Intensive Care Unit
PPROM	preterm prelabour rupture of membranes
RDS	respiratory distress syndrome
SGA	Small for gestational age

ABSTRAK

KAJIAN RETROSPEKTIF (2009- 2018) TENTANG KEHAMILAN KEMBAR YANG TIDAK BERKOMPLIKASI DI HOSPITAL SULTAN ISMAIL JOHOR BAHRU (HSIJB): HUBUNGAN ANTARA UMUR KANDUNGAN PADA WAKTU KELAHIRAN DAN KESAN KEPADA BAYI

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Pengenalan: Insiden kehamilan kembar semakin meningkat di seluruh dunia termasuklah di Malaysia. Ia melibatkan risiko yang tinggi sepanjang kehamilan kepada kedua- dua ibu dan bayi. Kajian ini bertujuan untuk mengetahui ciri- ciri ibu dan bayi bagi kehamilan kembar di Hospital Sultan Ismail Johor Bahru (HSIJB) dan untuk melihat hubungan kaitan antara usia kandungan kelahiran dengan kesan ke atas bayi tersebut dalam kehamilan kembar tanpa komplikasi.

Kaedah: Ini adalah kajian pemerhatian retrospektif terhadap wanita dengan kehamilan kembar monokorion dan dikorion tanpa komplikasi yang bersalin pada genap 36 minggu dan ke atas dari Januari 2009 sehingga Disember 2018 di HSIJB. Data dibahagikan kepada 3 kumpulan iaitu 36, 37 dan ≥38 minggu. Ciri-ciri demografi dan kehamilan ibu diperhatikan. Hasil utama adalah morbiditi komposit bayi, yang ditakrifkan sebagai mempunyai satu atau lebih daripada perkara berikut: kemasukan ke unit rawatan rapi bayi

(NICU), keperluan kepada alat bantuan pernafasan, Sindrom Masalah Pernafasan (RDS) dan kelahiran mati atau kematian perinatal dan neonatal. Umur kehamilan yang optimum untuk bersalin berpandukan kepada jenis kembar dianalisa berdasarkan morbiditi komposit bayi.

Keputusan: Seramai 949 bayi kembar dilahirkan di HSIJB dalam masa 10 tahun di mana 360 wanita dengan kehamilan kembar tidak berkomplikasi yang melahirkan 720 bayi menepati kelayakan untuk kajian ini (144 DCDA dan 216 MCDA). Bagi kembar DCDA, morbiditi komposit adalah paling sedikit dalam kumpulan 37 minggu, diikuti oleh kumpulan ≥ 38 minggu dan kemudian kumpulan 36 minggu. Untuk kembar MCDA pula, morbiditi komposit lebih tinggi dalam kumpulan 36 minggu, diikuti oleh kumpulan 37 minggu dan ≥ 38 minggu. Walau bagaimanapun, kaitan antara usia kehamilan semasa melahirkan dengan morbiditi komposit pada kembar MCDA adalah tidak signifikan.

Kesimpulan: Data kami menunjukkan bahawa usia kehamilan yang optimum untuk kelahiran bayi kembar DCDA yang tiada komplikasi adalah pada 37 minggu dan kembar MCDA pada ≥38 minggu.

KATA KEKUNCI: *kehamilan kembar tidak berkomplikasi; umur kandungan sewaktu kelahiran; kesan kepada bayi*

ABSTRACT

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Introduction: The incidence of twin pregnancy is increasing worldwide[1], and so does in Malaysia. It is associated with a higher risk of morbidity and mortality throughout pregnancy to both mother and fetus. This study aims to determine the maternal and fetal characteristic of twin pregnancies in Hospital Sultan Ismail Johor Bahru (HSIJB) and to observe the association between the gestational age at delivery and the delivery outcomes in uncomplicated twin pregnancies.

Methodology: This is a retrospective observational study of women with uncomplicated monochorionic and dichorionic twin pregnancies delivered at 36 completed weeks or beyond from January 2009 until December 2018 in HSIJB. The data is divided into 36 weeks group, 37 weeks group, and ≥38 weeks group. The maternal demographic and pregnancy characteristics were observed. The primary outcome was neonatal composite morbidity, which was defined as having one or more of the following: neonatal intensive care unit's admission, low Apgar score, the requirement of mechanical ventilator support,

respiratory distress syndrome, and stillbirth or perinatal/ neonatal mortality. The optimal gestational age for delivery according to chorionicity is determine based on the neonatal composite morbidity.

Results: A total of 949 sets of twins delivered at HSIJB over ten years, from which 360 women with uncomplicated twin pregnancies and 720 neonatal outcomes were eligible for the study (144 DCDA and 216 MCDA). In DCDA twins, the composite morbidity was least in the 37 weeks group, followed by the ≥ 38 weeks group and then 36 weeks group. On the contrary, more composite morbidity was seen in the MCDA twinning group at 36 weeks group, followed by the 37 weeks group and later in ≥ 38 weeks group. However, the association between the gestational age at delivery with composite morbidity in MCDA twin were insignificant.

Conclusion: Our data suggest that the optimal gestational age for delivery in uncomplicated DCDA twins was at 37 weeks and MCDA twins at ≥38 weeks.

KEYWORDS*: uncomplicated twin pregnancy; gestational age at delivery; neonatal outcomes*

INTRODUCTION

The incidence of twin pregnancy is increasing worldwide[1], and so does in Malaysia. It is mainly due to the use of the assisted reproductive technique (ART) whereby 24% of successful in vitro fertilization (IVF) procedures resulting in multiple pregnancy[2].

The incidence of twin pregnancy varies worldwide, the lowest is in Japan, 6.7 per 1,000 births, and the highest is in Nigeria, 40 per 1,000 births[3]. In England and Wales, the incidence is 16 per 1,000 births[3], and in the USA, it is 33.4 per 1,000 births[4]. While in Malaysia, the data from the National Obstetrics Registry of Malaysia (2010) showed the incidence of multiple gestations were 10.4 per 1,000 births (accounted for 1.04% of total birth) in which 97.8% were twin[5].

As widely known, twin pregnancies are associated with a higher risk of morbidity and mortality throughout pregnancy to both mother and fetus, and problems may extend into the postnatal period. The risks include an increase in premature birth (rate for singleton 28-36 weeks 8.7%, for twins 40.2%), increased in low birth weight (rate for singleton <2500g 5.8%, for twins 50.3%), intrauterine growth restriction (IUGR), congenital disabilities and birth complications[6]. Twins account for 10-14% of overall neonatal mortality[6]. A higher fetal death rate is also seen in monochorionic twins than in dichorionic twin pregnancies.

Healthcare professionals commonly acknowledge that twin pregnancies tend to deliver earlier than singleton pregnancies. It is also a widely held, although often contested, view among clinicians that perinatal outcomes in twin pregnancies worsen with increasing gestational age after 37 weeks. Evidence supports uncomplicated dichorionic twin delivery at 37 weeks' gestation and monochorionic twin delivery to be considered at 36

weeks' gestation to minimize stillbirth and newborn death[7,8]. As a result, women with twin pregnancies are often advised to undergo elective birth without any obvious indication[3].

LITERATURE REVIEW

A study by Soon Ruey et al. using the data from the National Obstetrics Registry of Malaysia in 2010 showed the fetal and neonatal morbidities were significantly increased in twin pregnancies compared to singletons. He found that the incidence of intrauterine fetal death (OR 4.77, 95% CI 2.91-7.79), prematurity (OR 8.09, 95% CI 6.41-10.21), low birth weight (OR 12.53, 95% CI 11.19-14.02), and low Apgar scores at one and five minutes (OR 2.95, 95% CI 2.53- 3.44 and OR 4.17, 95% CI 3.21-5.41) were higher as compared to singleton[5].

A prospective observational study on 171 sets of twins (73 DCDA and 93 MCDA twining) by Kuppannan K et al. noted that the most common medical disorders were associated with anaemia; (16% in DCDA and 18% in MCDA twin). Preterm labour occurred in 21.6% of DCDA and 28.6% of MCDA twins, while preterm prelabour rupture of membrane (PPROM) happened in 4.6% of DCDA and 6.4% of MCDA twins. The mean gestational age at delivery was 37 weeks in DCDA and 33 weeks in MCDA twins. The average weight of newborns was lower in MCDA pregnancies (1900 g vs 2240 g), whilst the incidence of discordant growth is 21.6% in MCDA as compared to 7.6% in DCDA twins. The mean Apgar score at 5 minutes of life was 8 in DCDA and 7 in MCDA twin with three babies required intubation. The rate of NICU admission in MCDA twin was 53.8%, mainly due to prematurity and in DCDA twin was 19.8%. There was no difference in the mean length of NICU stay for neonates > 36 weeks, which was 1.7 days. Lastly, the perinatal mortality rate in MCDA and DCDA twins was 7% and 1.3%, respectively[9].

A study conducted by Qazi G et al. of 161 multiple pregnancies (37.1 per 1,000 births) revealed that the four leading maternal adverse outcomes were anaemia (74.6%), preterm delivery (31%), pregnancy-induced hypertension (30%), and preterm prelabour rupture of membranes (26.2%). The median gestational age at delivery was 37 weeks, with the most common route of delivery was by caesarean section (53.3%). Meanwhile, the most common neonatal complication was low birth weight (LBW), and prematurity was the most common cause of neonatal death[10].

Dodd JM et al. conducted a randomized trial in 2012 on the timing of birth for twin pregnancies. A total of 235 women with uncomplicated dichorionic or monochorionic diamniotic twins were randomized to deliver at 37 weeks (n=116) versus at or after 38 weeks (n=119). Both groups showed no difference in neonatal and maternal outcomes, neither mode of delivery. However, he noted that there were statistically significant differences in mean birth weight between the two groups (2.74 kg vs 2.83 kg in the 37-week vs greater than 38-week groups)[8].

Another retrospective population-based analysis on the risk of stillbirth in multiple gestation pregnancies by Sairam S et al. showed the risk of stillbirth increased from 1:3333 at 28 weeks' gestation to 1:69 at or beyond 39 or more weeks' gestation. The risk of fetal death at 39 weeks' gestation in a twin pregnancy exceeded that of a post-term singleton pregnancy. He concluded that twin pregnancies should deliver between 37 to 38 weeks' gestation[11].

In a cohort study by Barigye O et al., he reviewed 151 uncomplicated monochorionic diamniotic pregnancies undergoing intensive ultrasound surveillance two weekly to calculate the risk of unexpected late fetal death. The study reported a prospective risk of stillbirth after 32 weeks of 4.3% (1 in 23)[12].

Danon D et al., in a systematic review and meta-analysis on nine studies of 119 cases, observed the gestational age-specific stillbirth rates after 24 weeks of gestation in uncomplicated monochorionic diamniotic twin pregnancies. The rate and risk of stillbirth were calculated in 2-week gestational age blocks and compared with controlled studies with dichorionic pregnancies concluded that the risk of stillbirth per monochorionic diamniotic pregnancy at 32, 34, and 36 weeks of gestation to be 1.6%, 1.3%, and 0.9%, respectively[13].

In 2016, Lee H et al. reported a retrospective cohort study regarding the gestational age at delivery and neonatal outcome in uncomplicated twin pregnancies delivered at or beyond 35 weeks of gestation for the year 1995 to 2013. A total of 697 twin pregnancies were included (171 monochorionic and 526 dichorionic twins), where conclusion the optimal gestational age for delivery was between 36 and 37 weeks gestation for both types of twin pregnancies[14].

Doss AE et al. conducted a retrospective study on gestational age at delivery and perinatal outcomes of twin gestations delivered at ≥36 weeks from 1991-2009. 377 sets of twins were included; 83% of them were dichorionic twins. The composite rate of perinatal morbidity and mortality, including perinatal death, respiratory distress, suspected sepsis, and need for neonatal intensive care was determined for weekly intervals from 36 to 39^{+} weeks. They suggested that the optimal time for delivery of twins is at 38 weeks or greater[15].

Ahmad F and Tarek Karkour suggested to deliver twins only at 38 completed weeks' gestation or later to avoid neonatal complications. These were based on their prospective cohort study over two years, including the twin with gestational age at delivery of at least 36 completed weeks, excluding the twins of mothers with chronic illness and those with

congenital anomalies. Out of 273 twins, 197 (72.2%) who met the inclusion criteria were classified into three groups according to the gestational age at delivery. Twins electively delivered had a worse outcome than those delivered spontaneously, and neonatal morbidity and maternal complications were higher in those delivered earlier. It is advisable to deliver twins only at 37 completed weeks' gestation or later to avoid neonatal complications[8].

STUDY JUSTIFICATION

This study aims to look for the neonatal complication in DCDA and MCDA twin pregnancies in HSIJB and later to determine the association between the gestational age and the delivery outcomes. It is conducted in this centre to get its local data and comparing findings with others, allowing better management of the patients.

OBJECTIVE(S)

GENERAL OBJECTIVE

1. To study the outcome of twin pregnancies in HSIJB.

SPECIFIC OBJECTIVES

1. To determine the maternal characteristic of twin pregnancies based on gestational age at HSIJB from 2009 to 2018.

2. To determine the association between gestational age at delivery and chorionicity with the neonatal outcome.

3. To determine the appropriate timing for twin delivery

METHODOLOGY

Study Type and Design

This study is a retrospective observational study. All cases of twin deliveries information during the study period of January 2009 until December 2018 were obtained from the electronic medical record (EMR) - Total Hospital System. The permission was received and granted by the local authority. A total of 949 twin deliveries were identified for a total of ten years of the study period.

The inclusion criteria were twin deliveries with gestational age at delivery at least 36 completed weeks. Twins of mothers with chronic illness, preterm prelabour rupture of membranes, placenta abruptio, placenta previa and those with monoamniotic twins, discordant twin, intrauterine growth restriction, twin to twin transfusion syndrome (TTTS), twin with major congenital anomalies and incomplete data were excluded in this study. The major fetal congenital malformation is defined as that requires medical or surgical treatment after birth. A discordant twin is defined as more than 20% weight differences between each twin. Perinatal outcome parameters (morbidity and mortality) were defined and evaluated.

From the 949 subjects, a total of 360 subjects (with a total of 720 neonatal outcomes) were eligible for the study after applying the inclusion and exclusion criteria. The data were categorized using an online form, then were classified into three groups according to the gestational age at delivery:

Group 1: Twin delivered at 36 weeks to 36 weeks 6 days' gestation

Group 2: Twin delivered at 37 weeks to 37 weeks 6 days' gestation

Group 3: Twin delivered at 38 weeks' gestation or beyond

The data collected were maternal demographic characteristics including age, ethnicity, parity, the use of the assisted reproductive technique (ART), gestational age at delivery, chorionicity, maternal risk factor including hypertensive disorder in pregnancy and diabetes mellitus in pregnancy, and also the mode of delivery. The mode of delivery was divided into vaginal delivery, caesarean section, and vaginal- abdominal delivery.

The data for the neonatal outcome includes gender, birth weight, Apgar score at one and five minutes, the requirement of admission to the neonatal intensive care unit (NICU) with its duration, the requirement of mechanical ventilator support, the presence of respiratory distress syndrome (RDS), and stillbirth or perinatal/ neonatal mortality with its cause were recorded. The neonatal composite morbidity is defined as having one or more of the following: neonatal intensive care unit's admission, low Apgar score, the requirement of mechanical ventilator support, respiratory distress syndrome, and stillbirth or perinatal/ neonatal mortality. The number of neonates with Low Birth Weight (LBW defined as any neonate weighing less than 2500 g at birth irrespective of the gestational age) were analyzed.

Data were analyzed using SPSS software version 24 to determine the association between gestational age of delivery with the most less neonatal composite morbidity. Neonatal composite morbidity is defined as having one or more of the following: 1. NICU admission, 2. using mechanical ventilator support, 3. RDS and 4. stillbirth or perinatal/ neonatal mortality.

Ethical approval was acquired from the Medical Research and Ethics Committee (Jawatankuasa Etika & Penyelidikan Perubatan), Ministry of Health [NMRR-19-490-46198] on 4th July 2019 (Appendix 2) and from Human Research Ethics Committee

(Jawatankuasa Etika Penyelidikan Manusia USM [JEPeM] Universiti Sains Malaysia) on 7th September 2020 [JEPeM Code: USM/JEPeM/20020084] (Appendix 3).

Study Population

Women with uncomplicated DCDA and MCDA twin pregnancies who delivered at or beyond 36 weeks' gestation in the Department of Obstetrics and Gynaecology, Hospital Sultan Ismail, Johor Bahru from 2009 until 2018.

Subject criteria

Inclusion Criteria

1. An accurate gestational age performed at first trimester ultrasound
2. Pregnancy ≥ 36 completed weeks gestation
3. Uncomplicated monochorionic and dichorionic twin pregnancies
4. Malaysian citizen

Exclusion Criteria

1. Twin-to-twin transfusion syndrome
2. Monoamniotic twins
3. Discordant twins
4. Intrauterine growth restriction
5. Preterm prelabour rupture of membranes
6. Placenta abruptio
7. Placenta previa
8. Hypertension (pre-eclampsia, eclampsia, superimposed pre-eclampsia, and chronic hypertension)
9. Diabetes (overt diabetes)
10. Presence of other severe maternal medical diseases
11. Fetal death before 36 weeks of gestation
12. Chromosomal anomalies
13. Major congenital malformation

Sample size calculation

The sample size (n) was calculated using the two proportions formula.

Percentage of twin having composite morbidity from previous literature: 5.9%

Based on a power of 80% (β=0.2), alpha of 0.05, an expected outcome in cases of 15%, the calculated sample size for each group is 176 patients. With allowing for 30% dropout, a final sample size of 252 per group will be used.

- P_0: 5.9%
- P_1: 15.0%
- a: 0.05
- P: 0.8
- Drop out: 30%

Sample size: 176, with drop out: 252

252 /arm x 3 arms (36w, 37w, ≥38w) = Total 756 samples

Study Flowchart

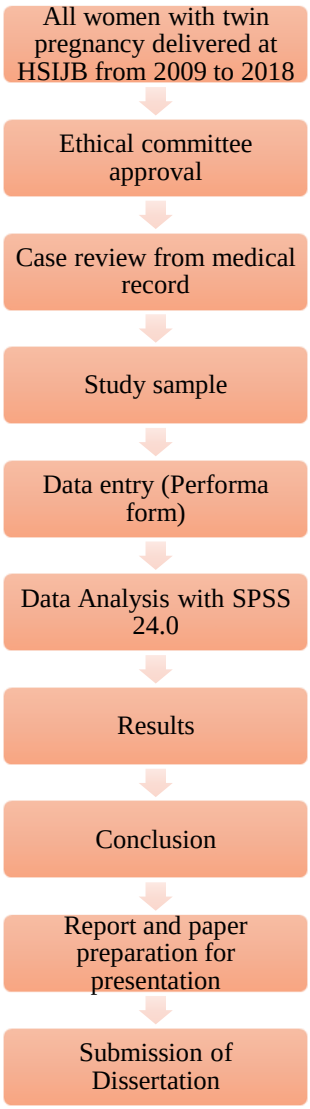

Figure 1: Study flowchart

Conceptual framework

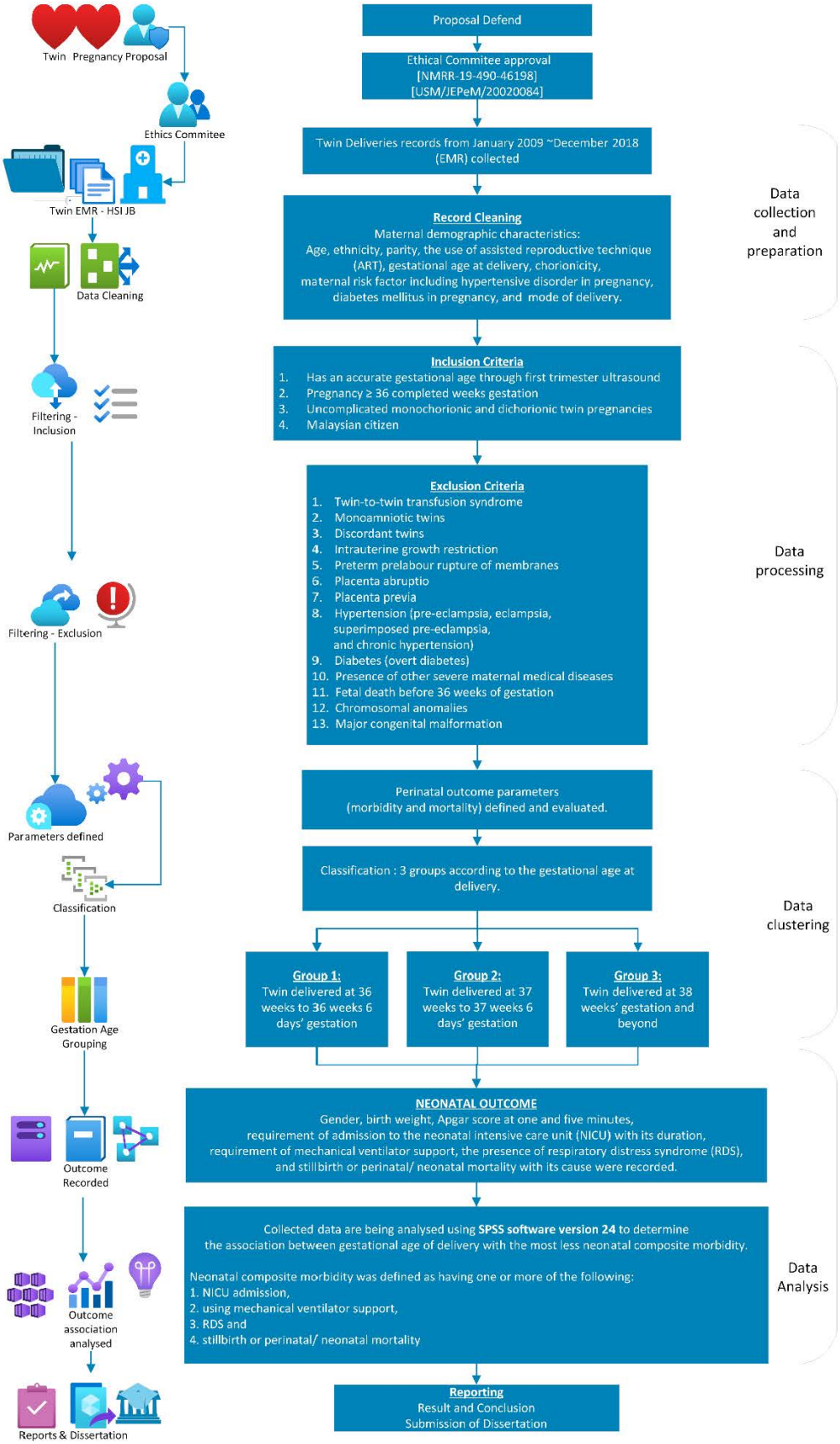

Figure 2: Conceptual framework

Data Analysis

Descriptive statistics were utilized for selected variables. The results were presented as frequencies and percentages for categorical data, T-test and One way ANOVA were used for the analysis of variance to compare continuous variables. Proportions (categorical variables) were compared using the Pearson chi-square test and Fisher exact test. Multiple logistic regression was used to see the association between gestational age and the composite morbidity outcome. The results were considered statistically significant if P-value <0.05. Statistical analysis will be conducted using IBM SPSS ver. 24.0.

MANUSCRIPT

TITLE PAGE

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