HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Reproduction

journal homepage: www.apjr.net

Original research http://dx.doi.org/10.1016/j.apjr.2015.06.007

Infant mortality in twin pregnancies following in-utero demise of the co-twin

Boubakari Ibrahimou[1*], Hamisu M. Salihu[2], Muktar H. Aliyu[3,4], Gary English[5], Getachew Dagne[6]

[1]*Florida International University, Robert Stempel College of Public Health & Social Work, Department of Biostatistics, 11200 S.W. 8th Street, AHC2 583, Miami, FL 33199, USA*

[2]*Baylor College of Medicine, Department of Family and Community Medicine, 3701 Kirby Drive, Suite 600, Houston, TX 77098, USA*

[3]*Department of Health Policy, Vanderbilt University, 2525 West End Avenue, Suite 750, Nashville, TN 37203, USA*

[4]*Department of Medicine, Vanderbilt University, 2525 West End Avenue, Suite 750, Nashville, TN 37203, USA*

[5]*Western Kentucky University, College of Health and Human Services, Department of Public Health, 1906 College Heights Blvd., Bowling Green, KY 42101, USA*

[6]*University of South Florida, College of Public Health, Department of Epidemiology and Biostatistics, 13201 Bruce B. Downs Blvd., MDC 56, Tampa, FL 33612, USA*

ARTICLE INFO

Article history:
Received 17 Mar 2015
Received in revised form 15 Apr 2015
Accepted 21 Apr 2015
Available online 24 July 2015

Keywords:
Surviving co-twin
Double programming
Twin conversion
Twin pregnancy
Mortality

ABSTRACT

Objective: To assess whether conversion from twin to singleton pregnancy following the demise of a co-twin influences survival.

Methods: This retrospective study compared the risk for neonatal, post-neonatal and infant death for converted co-twins versus unconverted co-twins using the US matched multiple file dataset for the period 1995–2000. We also examined the same risks for converted versus same-quantile co-twins, hazard ratios (HR) and 95% confidence intervals (CI) were computed using Cox Proportional Hazards models.

Results: The risk for neonatal (*HR* = 0.18, 95% *CI*: 0.09–0.34 and *HR* = 0.69, 95% *CI*: 0.50–0.96) and infant death (*HR* = 0.22, 95% *CI*: 0.12–0.42 and *HR* = 0.57, 95% *CI*: 0.42–0.77) were significantly lower for converted twins than for unconverted twins and same-quantile twins, respectively. For black compared to white, the risk for post-neonatal death increased by 89% (*HR* = 1.89, 95% *CI* = 1.03, 3.48), and 79% (*HR* = 1.79, 95% *CI* = 1.53, 2.09) for converted vs. unconverted and converted vs. same-quantile, respectively. For converted black, the risk for neonatal death decreased by 17% (*HR* = 0.83, 95% *CI* = 0.73–0.93) as compared to unconverted.

Conclusions: Risks for all mortality types were lower among converted co-twins than their unconverted or same-quantile counterparts. The lower neonatal and higher post-neonatal mortality among black require future research.

1. Introduction

Twin pregnancies are high-risk gestations with elevated perinatal mortality rates [1]. Twins, when compared with singletons, have a five-fold risk of fetal death, seven-fold elevated risk of neonatal death, and five-fold risk of infant death [2–4]. Twins also respond differently from singletons to interventions that are designed to lengthen the gestational age at birth [5,6]. Factors that impact fetal mortality risks include prenatal complications, maternal age, poor obstetric history and Assisted Reproductive Technology (ART) [1–6]. Twins face greater risks for low birth weight, preterm birth, long-term disability and early death than singletons [7].

Death of one of the twins in a multiple gestation can lead to severe complications in the surviving co-twin, especially in the second or third trimester [8]. The prognosis of the surviving twin in a dichorionic twin pregnancy is better than in a monochorionic twin gestation. The latter has more neurological complications such as neural tube defects, optic nerve hypoplasia, microcephaly, and hemorrhagic or hypoxic lesions of the white

*Corresponding author: Boubakari Ibrahimou, PhD, Assistant Professor, Florida International University, Robert Stempel College of Public Health & Social Work, Department of Biostatistics, 11200 S.W. 8th Street, AHC2 583, Miami, FL 33199, USA.
Tel: +1 305 348 7524;
Fax: +1 305 348 4901
E-mail: birahim@fiu.edu
Peer review under responsibility of Hainan Medical College

matter [9]. Other anomalies include bilateral renal cortical necrosis, unilateral absence of kidney, gastro intestinal tract atresia and hemifacial microsomia [9]. An important consequence of the demise of a co-twin is cerebral palsy in the surviving co-twin, which may be the result of prenatal damage arising from placental vascular anastomoses [10]. Fichera *et al*. [9] also reported a greater risk of perinatal mortality for the surviving co-twin in monochorionic vs. dichorionic pregnancies following a single intra-uterine, second or third trimester death.

As a result of in-utero demise of a co-twin, a twin pregnancy may sometimes be converted into a singleton gestation [5]. In these cases, the growth and development of the surviving singleton co-twin depends on the adaptive response and physiological process in the remaining pregnancy period. Salihu *et al*. studied the fetal programming switch process among surviving co-twins from a twin programming trajectory to that of a singleton during pregnancy [5].

It is well established that surviving co-twins have higher mortality rates than live-born twin pairs [11]. Surviving co-twins also bear a greater risk for later morbidity, including neurocognitive and behavioral problems [11–14]. It remains, however, unknown to what extent exposure to double programming in utero would impact subsequent morbidity and mortality of surviving co-twins. It will be interesting and useful to determine whether conversion to a singleton fetal programming pattern by surviving co-twins influences future survival. We are unaware of any twin study that has examined the contribution of double programming to early mortality among twins. Thus, the objective of this paper is to estimate the risk for neonatal, post-neonatal, and infant death among twins that were able to convert to singleton gestation as compared to those who do not within a large population-based sample of twins.

2. Materials and methods

The dataset from the "matched multiple birth file" prepared by the National Center for Health Statistics (NCHS), for the period 1995–2000, was used for this study. This dataset contains matched and linked data for multiple deliveries in the United States. The data files consist of individual records of live births and fetal deaths involving multiple deliveries. In the dataset, siblings were linked to their biological mothers through the use of a unique identifier. The primary outcomes of interest in this study were infant mortality (death of the infant from day 0 to day 364 after birth), neonatal mortality (death from day 0 to day 27 after birth) and post-neonatal mortality (death from day 28 to day 364 after birth).

Gestational age was determined as the time between the last menstrual period and the time of delivery of the baby (95% cases). When the menstrual estimate of gestational age was inconsistent with the birth weight (e.g. very low birth weight at term), a clinical estimate of gestational age on the vital records was used instead [15].The precision of using the gestational age as noted on the US birth certificate has previously been validated [16]. The exposure of interest in this study is conversion to singleton programming in the surviving co-twin following the demise of the other twin. The concept of change or turning points was used in order to estimate the point periods in-utero at which the "switch" from a twin to a singleton fetal programming sequence might have occurred following the demise of a co-twin. In a previous study, we reported findings showing that a critical in-utero mass has to be attained by the surviving co-twin for successful conversion to a singleton path during pregnancy. In that pioneer study, it is reported that a critical mass and a specific gestational age (change point) need to be attained for the conversion from twin to singleton to take place. Results of the study showed that a critical mass (80th percentile of the gestational age-specific birth weight distribution for twins of same sex pairs and 70th percentile for opposite sex pairs) have to be attained by the surviving co-twin for successful conversion to a singleton path during pregnancy. The threshold (change point) for the conversion of the surviving co-twin to a singleton programming sequence was approximately at the 27th week of gestation. A surviving co-twin satisfying these conditions will be referred to as "converted twin" throughout this manuscript. Otherwise, we will refer to the surviving co-twin as an "unconverted twin".

We consider two comparison groups for our study. In the first case we compare the survival of converted twins vs. unconverted twins. In second case comparison of survival between converted twins and same-quantile twins (co-twins who reached the same quantile of the birthweight distribution at the same gestational age, but who could not switch to singleton programming because their co-twin also survived and was delivered alive) is considered.

We selected viable births (20–44 weeks of gestation) for both converted, as well as unconverted and same-quantile twins. We further categorized twin clusters into three groups based on the presence or absence of a stillbirth (defined as intra-uterine fetal demise at 20 weeks' gestation):

1 Group A: all members were live births
2 Group B: one member was a live birth and the other a stillbirth (surviving co-twin model)
3 Group C: both members experienced a stillbirth.

We excluded Group C from further analysis. In the first comparison converted vs. unconverted only Group B is considered. In the second comparison converted vs. same-quantile twins, both co-twins from Group B and co-twins from Group A who reached the same quantile of the birth weight distribution at the same gestational age, but who could not switch to singleton programming because their co-twin also survived and was delivered alive were considered. The selection pathway for the co-twins used in this analysis is given in detail in Figure 1.

Study variables included in this analysis comprised: day of birth and death, mode of delivery (cesarean or vaginal), pregnancy and labor complications, method of delivery, maternal socio-demographics (race, age, marital status, educational level) and maternal lifestyle factors (smoking) and infant characteristics (e.g., sex). Maternal race was defined as black, white and others; maternal age was grouped as less than 18 years, 18–34 years and $\geq$35 years. Maternal education level was categorized into two groups: less than 12 years of education and $\geq$12 years. The study also determined the occurrence of maternal medical complications among both groups. Maternal complications considered included anemia, preeclampsia, chronic hypertension, placental abruption, diabetes and placenta previa.

The rate of infant mortality was computed by dividing the total number of deaths by the total number of live births and multiplying the outcome by 1000. Chi-square test was used to