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The Risk of Birth Defects in Multiple Births: A Population-Based Study

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Objectives: To determine if multiple births have higher risks of birth defects compared to singletons and to identify types of birth defects that occur more frequently in multiple births, controlling for seven sociodemographic and health-related variables. *Methods*: A retrospective cohort study was conducted of all resident live births in Florida during 1996–2000 using data from a population-based surveillance system. Birth defects were defined as in the 9th edition of the International Classification of Diseases—Clinical Modification (ICD-9-CM) code for the 42 reportable categories in the Centers for Disease Control and Prevention (CDC) Birth Defects Registry list and eight major birth defects classifications. Relative risks (RR) before and after adjusting for control variables and 95% confidence intervals (95% CI) were calculated. The control variables included mother's race, age, previous adverse pregnancy experience, education, Medicaid participation during pregnancy, infant's sex and number of siblings. *Results:* This study included 972,694 live births (27,727 multiple births and 944,967 singletons). Birth defects prevalence per 10,000 live births was 358.50 for multiple births and 250.54 for singletons. After adjusting for control variables, multiple births had a 46% increased risk of birth defects compared to singletons. Higher risks were found in 23 of 40 birth defects for multiple births. Five highest adjusted relative risks for birth defects among multiple births were: anencephalus, biliary atresia, hydrocephalus without spina bifida, pulmonary valve atresia and stenosis, and bladder exstrophy. Increased risks were also found in 6 out of 8 major birth defects classifications. *Conclusions*: Multiple births have increased risks of birth defects compared to singletons.

KEYWORDS: multiple births; birth defects; epidemiology; prevalence.

INTRODUCTION

The rate of multiple births has increased significantly in the United States over the past 20 years. The number of twin births increased 52% and triplets and other higher order multiple births increased 404% from 1980 to 1997 (1). Numerous studies have found that multiple births have a higher risk of preterm delivery, low birth weight, and neonatal mortality (2–5). Many epidemiological studies have observed that multiple births also have a higher risk of birth defects compared to singletons (6–18). For example, central nervous defects, cardiovascular defects, alimentary tract defects, ear defects, respiratory defects have all been observed more frequently among multiple births. Increased risks of specific birth defects among multiple births have been noted for macrocephaly, encephalocele, hydrocephaly, cleft lip and palate, anomalies of the diaphragm, cardiac septal

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defects, atresia or stenosis of the large intestine or anus, tracheoesophageal fistula, malformations of the alimentary tract, inguinal and umbilical hernias, and cystic kidney (11–15). While some studies had small sample sizes or focused on a limited number of birth defects (10, 13–18), most studies did not control for important sociodemographic and health-related variables (6–9, 11–20).

We extended the previous investigations of the associations between birth defects and multiple births in a large population-based cohort. We examined the 42 reportable birth defects used by the Centers for Disease Control and Prevention (CDC) and the 8 major birth defects classifications of these 42 reportable birth defects used by the Florida Birth Defect Registry (FBDR). Estimates of birth defects prevalence were calculated controlling for seven sociodemographic and health-related covariates. This study addressed two questions: 1) Is there a significantly higher risk of birth defects in multiple births compared to singletons after adjusting for important covariates? and 2) which types of birth defects are more likely to occur among multiple births compared to singletons?

MATERIALS AND METHODS

Data for this population-based, retrospective 5-year cohort study were extracted from statewide databases: Florida Birth Vital Statistics (FBVS) and the Florida Birth Defect Registry (FBDR). The FBDR data set was created by merging each of the following six data sets with the FBVS to identify children with birth defects: the Florida Agency for Health Care Administration (AHCA) Hospital Discharge Data, AHCA Ambulatory Data, Children's Medical Services (CMS) Minimum Data Set (comprising information from 14 medical subspecialty clinics), Regional Perinatal Intensive Care Centers (RPICC) Program Data Set, Early Intervention Program (EIP) Data Set, and AHCA Medicaid Eligibility Files. Each data set was first merged to FBVS to identify children with birth defects using a deterministic merging strategy based on the child's social security number, date of birth, name, sex, plurality, plurality order, address, county, mother's social security number, mother's name, father's social security number, and father's name. Then a deterministic strategy was followed for unmatched records, when social security numbers were missing. The total number of live births in Florida during 1996–2000 found in FBVS was 976,824. Approximately 99.6% children were matched to FBDR. For statistical modeling purposes, records with missing values for any of the covariates in the study were not included. Therefore 972, 694 live births (27,727 multiple births and 944,967 singletons) in Florida during 1996–2000 were included in this study.

In this study, the outcome variable was birth defect, defined as any congenital anomaly in the 9th edition of the International Classification of Diseases—Clinical Modification (ICD-9-CM) code (740–759.9) for the 42 CDC reportable birth defects. FBDR grouped these 42 major birth defects into 8 major birth defects categories. The birth defects were recorded within the child's first year of life.

The predictor variable of interest in this study was plurality with two levels: multiple births and singletons. The control variables were: 1) mother's race (White; Black; Other); 2) mother's age (less than 20 years; 20–34 years; greater than 34 years); 3) mother's previous adverse pregnancy experience (yes; no); 4) mother's education (less than high school; high school graduate; greater than high school); 5) Medicaid participation during pregnancy (yes, if mother received Medicaid during pregnancy; no, if mother was not eligible for Medicaid because family income exceeded 185% of the federal poverty level); 6) infant's sex (male; female); and 7)number of siblings (0; 1–2; greater than 2;).

Statistical Analysis

The Poisson regression models, with the number of children with birth defects as the outcome variable were fitted using the GENMOD Procedure in SAS. This method modeled the log of the probability of a birth defect as a linear function of sociodemographic and medical variables. Stepwise model building was employed. The models included all main effects of the explanatory factors. Based on the fitted model, the adjusted relative risk (ARR) and 95% confidence interval were estimated for each factor. The ARR reflects the independent effect of each factor on birth defects, controlling for the effects of all other explanatory factors.

RESULTS

The population proportion, birth defects prevalence, and adjusted relative risk of birth defects for categories of the seven sociodemographic and

Table I. The Population Proportion, Birth Defects Prevalence, and Adjusted Relative Risk of Birth Defects for Categories of Selected Sociodemographic and Health-related Variables in Multiple Births, Singletons, and the Tota Population (Florida, 1996–2000)

	Mutiple births		Singletons		Total population			
Sociodemographic and health-related variables	Proportion (%)	Birth defects prevalence	Proportion (%)	Birth defects prevalence	Proportion (%)	Birth defects prevalence	Adjusted RR	95% CI
Mother's race								
White	74.52	350.87	74.58	253.58	74.57	256.35	1.00	
Black	23.14	388.03	22.66	247.63	22.68	251.71	**0.93**	**0.91–0.94**
Other	2.34	309.12	2.76	192.32	2.75	195.15	**0.77**	**0.75–0.80**
Mother's age								
<20 years	7.06	459.65	13.16	247.44	12.98	250.73	**0.88**	**0.87–0.90**
20–34 years	72.99	356.74	73.55	243.72	73.53	246.91	1.00	
>34 years	19.95	329.11	13.29	291.33	13.49	292.93	**1.25**	**1.23–1.27**
Previous adverse Pregnancy experience								
No	68.15	356.67	72.69	242.48	72.56	245.54	**0.91**	**0.90–0.92**
Yes	31.85	362.40	27.31	271.99	27.44	274.98	1.00	
Mother's education								
Less than high school	15.37	415.20	21.36	273.29	21.19	276.22	**1.11**	**1.09--1.13**
High school	31.76	392.87	34.74	256.5	34.65	260.07	**1.06**	**1.04-1.07**
More than high school	52.87	321.35	43.90	234.75	44.16	237.71	1.00	
Medicaid participation During pregnancy								
No	60.57	311.44	54.46	227.72	54.63	230.36	1.00	
Yes	39.43	430.77	45.54	277.83	45.37	281.62	**1.25**	**1.24–1.27**
Infant's sex								
Male	49.84	395.80	51.25	292.38	51.21	295.25	**1.41**	**1.39–1.42**
Female	50.16	321.42	48.75	206.56	48.79	209.92	1.00	
Number of siblings								
0	21.70	365.57	42.45	257.29	41.86	258.89	1.00	
1–2	59.63	355.63	48.40	238.4	48.72	242.49	**0.89**	**0.88-0.90**
>2	18.67	359.42	9.15	283.4	9.42	287.69	**0.97**	**0.95–0.99**
Total	100.00	358.50	100.00	250.54	100.00	253.62		

Note. Multiple births, singletons and total population sizes are 27727, 944967, and 972694, respectively. Birth Defects Prevalence: birth defects per 10,000 live births. Adjusted RR: relative risk to each reference group of each variable adjusting for mother's age, race, previous adverse pregnancy experience, education, Medicaid participation during pregnancy, infant's sex, and number of siblings. Reference group for each variable is indicated in bold type. Significant relative risk and 95% confidence intervals are indicated in bold type.

health-related variables in multiple births, singletons and the total population in Florida from 1996 to 2000 are given in Table I. Multiple births were observed to have a 43% higher raw prevalence of total birth defects than singletons (358.50 vs. 250.54 per 10,000 live births).

The multiple births population had a higher proportion of black mothers, older mothers, mothers with previous adverse pregnancy experience, mothers with higher education, mothers with no Medicaid participation during pregnancy, mothers with more than one child, and female children. At every level of the control variables, multiple births had a higher prevalence of birth defects than singletons.

The adjusted relative risk and its 95% confidence interval of the total birth defects for each sociodemographic and health-related variables are also shown in Table I. All variables were significantly associated with birth defects.

Multiple births had a 46% increased risk of overall birth defects compared to singletons after adjusting for mother's race, age, previous adverse pregnancy experience, education, Medicaid participation during pregnancy, infant's sex, and number of siblings (Table II). Twenty three out of 40 specific birth defects in multiple births had higher risks compared to singletons after adjusting for seven covariates (Table II). Birth defects with the five highest adjusted RRs among multiple births were:

Table II. The Adjusted and Unadjusted Relative Risk of 42 CDC Reportable Birth Defects and 8 Major Birth Defects Classification by Plurality (Florida, 1996–2000)

	Multiple births		Singletons				
CDC reportable birth defects	*N*	Prevalence	*N*	Prevalence	Unadjusted RR	Adjusted RR	95%CI
Total birth defects	994	358.50	23675	250.54	1.43	**1.46**	**1.42–1.50**
Central nervous system defects	113	40.75	1785	18.89	2.16	**2.23**	**2.06–2.43**
Anencephalus	9	3.25	37	0.39	8.29	**7.44**	**5.39–10.25**
Encephalocele	3	1.08	78	0.83	1.31	1.55	0.94–2.56
Hydrocephalus without spina bifida	64	23.08	668	7.07	3.27	**3.43**	**3.06–3.84**
Microcephalus	16	5.77	698	7.39	0.78	0.81	0.65–1.00
Spina bifida without anencephalus	23	8.30	387	4.10	2.03	**2.09**	**1.74–2.52**
Chromosomal defects	43	15.51	1342	14.20	1.09	0.93	0.81–1.06
Down syndrome	38	13.71	1149	12.16	1.13	0.95	0.83–1.10
Trisomy 13	4	1.44	109	1.15	1.25	1.15	0.74–1.77
Trisomy 18	4	1.44	120	1.27	1.14	0.98	0.64–1.52
Gastrointestinal defects	78	28.13	2215	23.44	1.20	**1.27**	**1.15–1.40**
Biliary atresia	10	3.61	92	0.97	3.70	**3.54**	**2.66–4.72**
Esophageal atresia/tracheoesophageal fistula	16	5.77	222	2.35	2.46	**2.64**	**2.11–3.30**
Hirschsprung's disease (congenital megacolon)	10	3.61	201	2.13	1.70	**1.72**	**1.30–2.26**
Pyloric stenosis	31	11.18	1401	14.83	0.75	**0.81**	**0.69–0.95**
Rectal and large intestinal atresia/stenosis	11	3.97	336	3.56	1.12	1.15	0.89–1.50
Genital and urinary defects	202	72.85	5496	58.16	1.25	**1.31**	**1.23–1.39**
Bladder exstrophy	3	1.08	34	0.36	3.01	**2.81**	**1.67–4.71**
Hypospadias and Epispadias	114	41.12	3145	33.28	1.24	**1.33**	**1.23–1.45**
Obstructive genitourinary defect	73	26.33	2109	22.32	1.18	**1.19**	**1.07–1.31**
Renal agenesis/hypoplasia	12	4.33	316	3.34	1.29	**1.29**	**1.01–1.66**
Heart defects	526	189.71	10762	113.89	1.67	**1.65**	**1.59–1.71**
Aortic valve stenosis	4	1.44	129	1.37	1.06	1.01	0.66–1.56
Atrial septal defect	290	104.59	6258	66.22	1.58	**1.56**	**1.48–1.64**
Coarctation of aorta	18	6.49	392	4.15	1.56	**1.56**	**1.27–1.91**
Common truncus	6	2.16	90	0.95	2.27	**2.20**	**1.53–3.15**
Ebstein's anomaly	0	0.00	57	0.60	0.00	0.00	NA
Endocardial cushion defect	8	2.89	330	3.49	0.83	0.75	0.56–1.02
Hypoplastic left heart syndrome	7	2.52	217	2.30	1.10	1.10	0.79–1.52
Pulmonary valve atresia and stenosis	83	29.93	930	9.84	3.04	**2.97**	**2.69–3.27**
Tetralogy of Fallot	27	9.74	445	4.71	2.07	**2.06**	**1.73–2.44**
Transposition of great arteries	13	4.69	343	3.63	1.29	**1.28**	**1.01–1.64**
Tricuspid valve atresia and stenosis	8	2.89	130	1.38	2.10	**2.00**	**1.47–2.74**
Ventricular septal defect	194	69.97	4181	44.24	1.58	**1.57**	**1.48–1.68**
Musculoskeletal defects	58	20.92	2445	25.87	0.81	0.92	0.82–1.03
Congenital hip dislocation	19	6.85	1281	13.56	0.51	**0.56**	**0.46–0.68**
Diaphragmatic hernia	16	5.77	251	2.66	2.17	**2.28**	**1.83–2.84**
Gastroschisis/Omphalocele	22	7.93	629	6.66	1.19	**1.53**	**1.27–1.84**
Reduction deformity: lower limbs	1	0.36	140	1.48	0.24	0.24	0.10–0.57
Reduction deformity: upper limbs	5	1.80	200	2.12	0.85	0.86	0.58–1.26
Oral clefts	55	19.84	1463	15.48	1.28	**1.29**	**1.15–1.45**
Choanal atresia	4	1.44	151	1.60	0.90	0.92	0.60–1.42
Cleft lip with and without cleft palate	35	12.62	854	9.04	1.40	**1.44**	**1.25–1.67**
Cleft palate without cleft lip	16	5.77	461	4.88	1.18	1.13	0.91–1.41
Other defects	24	8.66	611	6.47	1.34	**1.24**	**1.04–1.49**
Aniridia	0	0.00	12	0.13	0.00	0.00	NA
Anophthalmia/microphthalmia	3	1.08	94	0.99	1.09	1.13	0.69–1.87
Anotia/microtia	3	1.08	59	0.62	1.73	**1.89**	**1.14–3.13**
Congenital cataract	6	2.16	113	1.20	1.81	**1.92**	**1.34–2.74**
Fetal alcohol syndrome	12	4.33	343	3.63	1.19	1.03	0.80–1.32

Note. Prevalence: birth defects prevalence per 10,000 live births. Number of the major birth defects classification is not the sum of the specific birth defects in this classification, since a child could have more than one specific birth defect in this classification. Adjusted RR: relative risk to singletons adjusting for mother's age, race, previous adverse pregnancy experience, education, Medicaid participation during pregnancy, infant's sex, and number of siblings. Significant relative risk and 95% confidence intervals are indicated in bold type. NA: Confidence intervals for Ebstein's anomaly and Aniridia were not availabe, since multiple births had no such birth defects.

Table III. The Mean and Standard Deviation of Birth Weight and Gestational Age by Plurality (Florida 1996–2000)

Plurality	Birth weight (g) Mean ± SD	Gestational age (weeks) Mean ± SD
Singleton	3322.34 ± 578.31	38.75 ± 2.11
Twin	2339.40 ± 655.24	35.19 ± 3.42
Triplet	1671.37 ± 578.80	31.96 ± 3.40
Quadruplet and more	1292.76 ± 445.23	29.86 ± 2.77

anencephalus, biliary atresia, hydrocephalus without spina bifida, pulmonary valve atresia and stenosis, and bladder exstrophy (Table II). Six out of eight major birth defects classifications in multiple births had increased risks (Table II). Unadjusted relative risks are also shown in Table II. Adjusted RRs of several birth defects are very different compared to unadjusted RRs.

Mean birth weight and gestational age and their standard deviations for singletons, twins, triplets, and quadruplets and more are given in Table III.

DISCUSSION

This study is consistent with other previous studies which have found that multiple births had increased risks of birth defects compared to singletons (6–9, 11–18). However, few of these studies had large enough sample sizes to explore the wide range of specific birth defects in this study while controlling for important covariates.

Our finding that multiple births were more likely than singletons to have a higher prevalence of birth defects within 1 year of delivery was consistent with the results of Mastroiacovo and Li, who investigated birth defects prevalence in multiple births compared to singletons in a large population (7, 8). Furthermore, many of the specific birth defects that were found to be more likely in multiple births in this study were also observed in Mastroiacovo and Li studies (7, 8). For example, this study found an association between anencephalus and multiple births that was consistently found in other studies (8, 12). The association of ventricular septal defect and multiple births that was observed in this study was also confirmed by other studies (7, 8). This study found that multiple births had higher risks in atrial septal defect, coarctation of aorta, tetralogy of Fallot, Hirschsprung's disease, renal agenesis, hypospadias and epispadias, and obstructive genitourinary defect, which were also confirmed in Li's result (8). The associations of diaphragmatic hernia, cleft lip with and without cleft palate, and multiple births that was found in this study was consistent with Mastroiacovo's study (7). However, this study also found associations of biliary atresia, gastroschisis/omphalocele, anotia/microtia, congenital cataract, tricuspid valve atresia and stenosis, bladder exstrophy, esophageal atresia, hydrocephalus without spina bifida, spina bifida without anencephalus, and multiple births, which were not observed in Mastroiacovo's and Li's studies (7, 8). Some studies found contradictory conclusions that total congenital malformations were not significantly more frequent in twins (19, 20). However, one study compared twins with the total newborn population (20). Another study explained that the relatively low incidence of malformations in twins may be due to a significantly low rate of congenital hip dislocation (RR = 0.4) in twins (19). Our results showed that multiple births had a lower risk of congenital hip dislocation, a finding confirmed in other studies (8, 12, 19). Multiple births were also observed to have a slightly lower risk of pyloric stenosis.

Multiple births are more likely to be delivered early and to weigh less at birth compared to singletons (2, 3). Our study agreed with these findings. For example, the mean birth weight of a twin was 1000 g less than that of a singleton (mean birth weight for singletons: 3322 g, twin: 2339 g) and the mean gestational age was 4 weeks less (mean gestational age for singleton: 39 weeks, twin: 35 weeks). One paper controlled for gestational age and birth weight to see if there were any differences in cerebral palsy rates between multiple births and singletons within subgroups defined by gestational age (<28, 28–31, 32–36, and ≥37 weeks) and birth weight (<1000, 1000–1499, 1500–2499, and ≥2500 g) (10). The results showed no significant differences in cerebral palsy rates between multiple births and singletons for each subgroup of gestational age or birth weight. The same grouping for gestational age and birth weight was used in this study to see if any differences in total birth defects between multiple births and singletons occurred in each subgroup. The results showed that multiple births had a lower risk of birth defects in each subgroup compared to singletons. So, although when controlling for birth weight and gestational age, multiple births had a lower risk for birth defects than singletons, without those controls, multiple births were observed to have higher risks of birth defects than singletons. Further study is

needed to find appropriate methods to control for birth weight and gestational age when investigating the associations of birth defects and multiple births.

The mechanisms by which multiple births increase the risks of some birth defects are still not clear. There are several possible explanations for higher risks of birth defects in multiple births. One explanation is that the crowded intrauterine space may cause positional defects so that multiple births are more likely to have mechanically-induced defects (21). Another explanation is that mothers with multiple fetuses may lack sufficient nutritional supply so that the normal fetal development is adversely affected (8). A third explanation is that the fertilization and reproductive technologies which account for increased number of multiple births may increase spontaneous mutations and some birth defects (7).

This study extends the small number of studies that have investigated the risks of multiple births to a large range of birth defects in a large population-based cohort. Furthermore, the prevalence estimates of birth defects were adjusted for seven covariates (mother's race, age, education, previous adverse pregnancy experience, Medicaid participation during pregnancy, infant's sex, and number of siblings). The previous studies have shown that advanced maternal age (35–40 years), black mothers, low socioeconomic status of mothers, adverse previous pregnancy experience, and male children were associated with higher risks of birth defects (22–28). This study demonstrated that all seven sociodemographic and health-related variables were significantly associated with birth defects. Therefore, it is essential to control for sociodemographic and medical variables in any assessment of the role of plurality in the prevalence of birth defects. The adjustments for seven covariates resulted in several very different adjusted RRs from unadjusted RRs. For example, the adjusted RR of gastroschisis/omphalocele was 28% larger than the unadjusted RR. The adjusted RR of anencephalus was 10% smaller than the unadjusted RR.

This study has several limitations: 1) The Florida birth defect registry did not include data for birth defects resulting in natural and spontaneous terminations, stillbirths, and miscarriages; and 2) children born in Florida, who out-migrated from the state before their first birthday were not included.

In conclusion, this study rigorously estimated the risks of 42 specific birth defects and 8 major birth defects classifications in multiple births compared to singletons in a large population-based cohort controlling for seven important sociodemographic and health-related covariates. Twenty three specific birth defects and six major birth defects categories had higher risks in multiple births. Multiple birth is unequivocally a risk factor of birth defects. Further clinical and biological studies are needed to understand the mechanisms by which the risk of birth defects is elevated in multiple births.

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