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Prevalence and Descriptive Epidemiology of Omphalocele in Iowa, 2000-2019

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Prevalence and Descriptive Epidemiology of Omphalocele in Iowa, 2000-2019

By

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Bachelor of Public Health

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Abstract

Prevalence and Descriptive Epidemiology of Omphalocele in Iowa, 2000-2019
By Sashawn Lawrence

Background: Omphalocele is an abdominal wall defect in which all or part of the small intestine exists outside of the abdomen in a membranous sac. The epidemiology of omphalocele is not well-understood, with previous reports differing on prevalence estimates and child and parental characteristics associated with this defect. The aim of this study is to use data from a 20-year population-based sample of children with omphalocele to examine prevalence, as well as associations between omphalocele and selected child, maternal, and paternal risk factors.
Methods: For children delivered in Iowa during 2000-2019, data for children with omphalocele (n=235) were obtained from the Iowa Registry for Congenital and Inherited Disorders and for all live births and fetal deaths (n=781,113) from the Iowa Department of Public Health. These data were used to estimate omphalocele prevalence and associations with selected child, maternal, and paternal factors using log-binomial regression models. Crude and adjusted prevalence ratios and 95% confidence intervals were estimated for all case children and for those with a definite diagnosis (prenatal diagnosis and postnatal diagnosis), isolated omphalocele (no additional, major birth defect) and nonsyndromic omphalocele (no monogenic or chromosomal disorder).
Results: Prevalence (per 10,000 live births and fetal deaths) of omphalocele during 2000-2019 was 3.01 (95% confidence interval = 2.65, 3.42). The estimated annual percentage change was 1.56% per year (95% confidence interval = -0.69, 3.86). In multivariate analysis, male sex, plurality ≥ 2, advanced maternal age (≥ 35 vs. < 35 years), and other maternal race/ethnicity (vs. non-Hispanic White) were observed to be associated with an increased risk, whereas non-Hispanic Black and Hispanic maternal race/ethnicities were associated with a reduced risk. Subgroup analysis for case children with definite diagnosis and for those that presented with isolated or nonsyndromic omphalocele tended to yield similar results.
Conclusion: This is the longest temporal examination of population-based prevalence estimates for omphalocele in the US. Findings offer an increased understanding of selected child, maternal, and parental antecedents for omphalocele. Future studies with larger, more racially/ethnically diverse samples and data on additional risk factors are needed to understand the etiopathogenesis of this birth defect.

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Table of Contents

CHAPTER I

PUBLIC HEALTH SIGNIFICANCE

Omphalocele is an abdominal birth defect in which all or part of the small intestine exists outside of the abdomen in a membranous sac [1]. A small omphalocele is defined as a defect size of <5 cm and the absence of a protruded liver, whereas a giant omphalocele is ≥5cm with at least some protrusion of the liver through the omphalocele sac [2, 3]. A ruptured omphalocele occurs when the sac disintegrates causing the viscera to be exposed to the amniotic fluid [4, 5]. Ruptures can be defined as primary (prenatal) or secondary (postnatal) and can occur in both small and giant cases of omphalocele [4, 6].

The global prevalence of omphalocele is estimated at 3.4 per 10,000 live births [7], with some national studies reporting prevalence estimates ranging from 1.0 to 3.8 per 10,000 births [8-11]. A recent population-based study in the United States (US) that used data from the National Birth Defects Prevention Network (2012-2016) reported a population prevalence of 2.1 per 10,000 live births (95% confidence interval (CI)=2.0, 2.22) [10].

Despite being a rare disease, omphalocele is one of the most common and life threatening forms of anterior abdominal wall defects [12]. Approximately 5-60% of omphalocele cases result in premature delivery, and 5-35% result in intrauterine growth restriction [13, 14]. Survival among infants with isolated omphalocele is higher than those with other co-occurring major birth defects [15, 16]. Between 50-70% of all cases of omphalocele present with another birth defect. This includes a variety of common chromosomal related syndromes, such as Trisomies 13, 18, and 21 and Turner syndrome, [17-23], as well as other well-defined syndromes, such as Beckwith Wiedemann syndrome [7, 24]. Estimated survival of fetuses with omphalocele in the US ranges from 23-52% due to high rates of elective termination [25, 26]. However, infants with

isolated omphalocele may have up to 96% survival [27, 28]; those diagnosed prenatally have estimated survival ranging from 20-50% regardless of isolated or multiple status [15, 25, 29].

Both small and giant omphalocele can be surgically corrected; however, long-term care may differ depending on the size of the omphalocele [12, 30]. Ruptured omphalocele can also be corrected, however, due to its complexity, ruptures are often associated with longer hospital stays and are more resource intensive compared to small or giant omphalocele without ruptures [4]. Estimated total expenditures to treat omphalocele in the US has ranged from $28 million for direct medical expenses in 1992 [31] to $59.9 million for hospitalizations in 2003 [32]. The average length of hospital stay for a child with omphalocele was 32.5 days, and the mean cost of the stay was $141,724 in 2003 [32].

Although omphalocele has been associated with several single gene and chromosomal disorders, there is also evidence of a multifactorial etiology. As a further step toward improved understanding of the etiopathogenesis of omphalocele, the proposed case-cohort study will compare selected characteristics for a statewide sample of individuals with omphalocele delivered during 2000-2019 and identified by the Iowa Registry for Congenital and Inherited Disorders with those for all Iowa live births and fetal deaths during that time. With these data, we aim to examine an overall prevalence and temporal changes in prevalence for omphalocele spanning one of the largest time periods studied to date for this defect. We also aim to examine selected infant, maternal, and paternal risk factors associated with omphalocele in Iowa using a case-cohort design. Findings from our study will provide a well-defined, population-based sample to serve as a foundation for future studies of the etiopathogenesis of omphalocele.

CHAPTER II

BACKGROUND AND LITERATURE REVIEW

Introduction

Omphalocele, also known as exomphalos, is a defect of the abdominal wall in which all or part of the small intestine exists outside of the abdomen in a membranous sac [1]. Omphalocele can be classified as small, giant, or ruptured depending on the size of the defect in the abdominal wall and how much of the liver is present in the membranous sac [33-36]. At birth, a ruptured omphalocele presents like gastroschisis even though the embryology of each are different [5]. As a result, a prenatal ruptured omphalocele typically needs to be ascertained by looking for remnants of a membranous sac, presence of abdominal wall muscle, normal insertion of an umbilical cord or other distinguishing factors [5, 37]. A postnatal omphalocele rupture can occur if an infant with giant omphalocele is mishandled or birthed vaginally [14].

There are three recognized subtypes of omphalocele based on the site of defect and umbilical cord insertion: 1) central, 2) epigastric (cranial), and 3) hypogastric (caudal) [12, 25]. Central omphalocele occurs at the midline of the abdominal wall, typically situated on or adjacent to the umbilical cord [12]. Epigastric omphalocele occurs in the upper abdominal wall and does not involve the umbilical cord [12]. Hypogastric omphalocele is located on the lower abdominal wall and usually associated with urorectal anomalies [12].

Omphalocele often presents with other major birth defects [10], including cardiac and musculoskeletal defects, which are the main cause of mortality among affected infants [38-48]. Co-occurring defects are present among approximately 40-80% of infants diagnosed with omphalocele [20, 42, 49]. A recent US population-based prevalence study reported that

approximately 78% of omphalocele infants presented with co-occurring birth defects, including 17% with co-occurring chromosomal defects [50].

Prevalence

Three recent population-based studies used data from the US National Birth Defects Prevention Network (NBDPN) to estimate prevalence of omphalocele. Marshall et al. (2015) estimated the prevalence of omphalocele at 1.92 per 10,000 live births from 1995-2005, with no consistent trend over the study period [50]. St. Louis et al (2017) used data that overlapped with those from Marshall et al (2015) and reported prevalence to be 1.0 per 10,000 live births (95% CI=0.97, 1.08) during 1999-2007; trend analysis showed a small increase in the average annual percent change among mothers 24 years or younger and among non-Hispanic Black mothers [9]. Stallings et al. (2019) analyzed the most recent and largest study to date in the US, estimating a prevalence of 2.1 per 10,000 live births (95% CI=2.0, 2.2) for 2012-2016; trends in prevalence were not examined [10].

Embryology

Omphalocele occurs due to an error in embryonic development in the abdominal midline causing a herniated anterior abdominal wall [12, 51, 52]. An incomplete divergence of mesodermal somites into myotomes and a failed closure at the right and left lateral mesodermal folds results in an opening at the umbilical ring [53]. The membranous sac containing abdominal organs, protrudes through the opening after the organs fail to rotate and return back into the abdominal cavity [7, 12]. The size of and type of omphalocele varies widely depending on the time point in gestation that the abdominal content restriction occurs [2].

There is no clear consensus on the developmental mechanisms that lead to omphalocele [54, 55]. Suggested mechanisms include failure of the bowel to contract to the abdomen, complete failure of the lateral-body fold migration and body wall closure, and presence of primitive body stalk [54-56]. Of the mechanisms proposed, the current most widely accepted is a combination of the embryonic dysplasia [57] [58] and embryonic dysgenesis [59] [60]. Embryonic dysplasia is thought to arise from early germinal disc defects that cause malformations in the amniotic band sequence, whereas embryonic dysgenesis is thought to occur due to malformations in the ectodermal placodes in early development that cause malfunctions in the embryonic folding process [55].

Prenatal diagnosis

Omphalocele is often diagnosed prenatally [2]. Fetal ultrasound, computer tomography, magnetic resonance imaging, and abdominal x-ray can all be used to diagnose omphalocele [12, 26, 39, 52, 61]. Fetal ultrasound is the most widely used method of diagnosis, accounting for about 67% of all cases diagnosed [12, 52]. Omphalocele can also be screened by assessing maternal serum alpha-fetoprotein and measuring the dosage of acetylcholinesterase in the amniotic fluid [12, 52]. In the 20th century, most omphalocele cases were detected during the second trimester [2, 54]; however, improvements in ultrasound technology now allows almost one-half of all prenatal diagnoses to occur as early as 11-14 weeks gestation using the nuchal translucency ultrasound screening test [2, 54]. After identification of a membranous sac outside the abdomen indicating an omphalocele, further tests including additional fetal ultrasound and fetal echocardiogram [2], are conducted to determine if there are any accompanying defects [62].

A fetal karyotype may also be obtained to collect more information on any co-occurring defects [2, 35, 62].

Treatment

Surgical treatment of omphalocele depends on the defect subtype and size, along with the size of the infant and whether there are accompanying major birth defects [14]. If the omphalocele is not ruptured, surgical intervention does not need to be immediate, and a complete evaluation of the infant can precede [14]. For infants with a small omphalocele and in good health, a definitive operative surgery can be performed to close the herniated viscera [14, 63]; surgery is recommended with caution for those with a giant omphalocele particularly when the defect cannot be easily closed or the surgery may pose serious risks [14]. Infants with small omphalocele rarely need long-term care unless other major chromosomal or structural defects are present [30]. Conversely, approximately 60% of patients with giant omphalocele will require long-term care, particularly care related to respiratory insufficiency [64]. Optimal surgical procedures for giant omphalocele are controversial [65]. The sac can be closed during the neonatal period or later in childhood [65]; however, because the degree of viscera outside the abdomen is greater than that for a small omphalocele, a giant omphalocele often is closed in stages to prevent abdominal compartmental syndrome that can lead to multisystem organ failure and death [65, 66].

There are two main types of staged closure techniques for omphalocele: 1) advancing the skin flaps to cover the defect without opening the amniotic sac [67] and 2) promoting epithelization of the sac by applying topical agents [68-73]. The skin flap technique is completed during the neonatal period and eliminates the need for another surgery to cover the omphalocele

later in life [65]. Additionally, the protective barrier that the intact amniotic sac provides, may limit risk of infection and development of adhesive bowel obstruction after closure [65, 74, 75]. Despite these benefits, the epithelization technique is more common because of its proven safety and effectiveness [14, 76, 77]; however, with this technique, an operation is required later in childhood to close the omphalocele [65]. Delayed closure of a giant omphalocele is generally associated with higher rate of neonatal morbidity and in some cases prolonged hospital stays and longer ventilation use compared to early closure [27, 64, 65, 71, 78, 79].

Treatment for a small, ruptured omphalocele usually occurs using a primary closure procedure; however, the surgical intervention has to be more urgent than that scheduled for an small, unruptured omphalocele [4]. A ruptured giant omphalocele requires the most intensive care and often requires multiple procedures to close the opening [4]. These procedures may include a fascial bridge, silo with delayed closure, epithelization with topical agents, and negative pressure wound therapy can facilitate closure [4]. Potential complications can occur from many of these methods of repair. The most common complication is sepsis. Depending on the repair method, other complications can include hernias, enterocutaneous fistula formation, hypothyroidism, and hyponatremia [4, 80, 81]. Overall, the prognosis for giant and ruptured omphalocele is poor whereas that for small omphalocele is good [64].

Mortality

Overall, studies report that approximately 12% of pregnancies with omphalocele result in neonatal death and 39-41% result in stillbirth or termination of pregnancy [82-84]; however, these estimates may differ depending on the size of the omphalocele and type of co-occurring defects present [82]. For example, mortality among neonates with giant omphalocele has been

reported to range from 10-25% [35, 64, 65, 76]; data on whether this demise is directly related to the severity of giant omphalocele or associated defects are lacking. Survival for neonates with omphalocele also largely depends on post-operative care and resources, especially for those with giant omphalocele [24]. Due to lack of proper equipment and access to safe anesthesia and dedicated neonatal intensive care units, many low- and middle-income countries have lower rates of survival for neonates presenting with omphalocele compared to high income countries [24, 85-88]. The overall mortality of omphalocele in low and middle income countries ranges from 30-45% [24].

Previous studies have shown that infants born to non-Hispanic Black mothers experience higher infant mortality attributable to birth defects than non-Hispanic White mothers [10, 89-91]. However, in comparing survival estimates among a sample of infants born with omphalocele during 1999-2007, Wang et al. observed that survival for neonates and infants born to non-Hispanic Black mothers was 80.2 and 74.6 respectively, higher than those born to non-Hispanic White (79.6 and 73.9 respectively) and Hispanic (75.4 and 66.2 respectively) mothers [92].

Etiology

Genetic factors

Omphalocele often presents with chromosomal defects, different types of polymalformative syndromes, genetic syndromes, and other gene mutations [12]. Omphalocele may co-occur with chromosomal defects with estimates ranging from 38-67% of all diagnoses [25, 51, 93]. Trisomy 18 is the most common co-occurring chromosomal defect followed by trisomy 13 [13, 25, 94]. Omphalocele often occurs as part of a recognized syndrome, including Beckwith-Wiedemann syndrome, amniotic band syndrome, Shprintzen syndrome, Carpenter syndrome, Goltz

syndrome, Marshall-Smith syndrome, schisis association, OEIS syndrome (omphalocele, exstrophy of the bladder, imperforate anus, spinal defects), Meckel-Gruber syndrome, otopalatodigital type II syndrome, pentalogy of Cantrell, and CHARGE syndrome 21 [21-23].

Non-genetic factors

a. Infant Factors

Sex

Omphalocele tends to have a higher prevalence among male infants compared to female infants [9, 10, 50, 95-102]. Each of the three recent NBDPN studies mentioned previously reported higher prevalence among males than females [9, 10, 50], although one study [9] reported that the average annual percent change in prevalence over the study period (1999-2007) was greater for females compared to males. Despite the male predominance reported in these more recent studies, some earlier studies observed no excess of males with omphalocele [103, 104].

Multiple Gestation

Studies have consistently reported a higher prevalence of omphalocele among offspring of women with multiple gestation compared to singletons [50, 84, 105-110]. A NBDPN study using data from 1995-2005 reported a prevalence ratio of 2.22 (95% CI= 1.85, 2.66) when comparing women with multiple gestation to those with singleton pregnancies [50]. Using data from the National Birth Defects Prevention Study (NBDPS, 1997-2003), Mac Bird et al. conducted a risk factor study to investigate associations between maternal exposures and demographic factors and omphalocele [109]. These investigators reported nearly three times increased odds of omphalocele among mothers with multiple births compared to those with a singleton birth (aOR= 2.93, 95% CI= 1.43, 6.00) [109]. Additional studies have reported associations between multiple gestation and nonsyndromic omphalocele [105-108].

Birth Weight and Gestational Age

Studies have shown that the risk of birth defects is significantly higher for infants born prematurely compared to those carried to term [84, 111-114]. This risk has also been reported for omphalocele [10, 50, 105, 109]. In a recent study, Miquel-Verges et al. [115] observed increased odds of being diagnosed with an omphalocele among preterm infants (24-28 weeks [12.6, 95% CI= 5.4, 29.6], 29-33 weeks [7.8, 95% CI= 4.8, 12.7], and 34-36 weeks [3.8, 95% CI= 2.7,5.4]) compared to those born at term (37-41 weeks). NBDPN data (2012-2016) showed that 43.3% of individuals born with omphalocele were delivered preterm (20-36 weeks), and 22.9% of all individuals were considered early preterm (22-33 weeks) [10]. The challenge in interpreting birth weight and gestational age as risk factors for omphalocele is the difficulty in disentangling the contribution of the defect to these adverse birth outcomes [116].

b. **Maternal Factors**

Race/Ethnicity

Multiple studies have reported an increased risk of omphalocele among infants born to non-Hispanic Black mothers [9, 10, 50, 117, 118]. A large, US population-based study reported that the prevalence of omphalocele was highest among infants born to non-Hispanic Black mothers compared to those born to non-Hispanic White mothers with inverse risks reported for infants born to Hispanic, non-Hispanic Asian/Pacific Islander and non-Hispanic American Indian/Alaska Native mothers [118]. Data are limited, however, in exploring associations between race/ethnicity across omphalocele phenotypes (i.e. isolated vs. non-isolated).

Age

Most studies have reported maternal age as a risk factor for omphalocele, particularly among mothers at the extremes of young and advanced maternal age [10, 50, 84, 95, 96, 119-121], with advanced maternal age most often reported [10, 50, 84, 95, 96, 105, 119, 121]. Two recent NBDPN studies reported that the prevalence of omphalocele was highest among women of advanced age (≥35 years) followed by women of young maternal age (<20 years) [10, 50]. One of these studies [50] also reported that chromosomal defects were more likely to occur among infants of mothers ≥35 years; however, this study was limited to live births.

Education

The association between maternal education and omphalocele has received limited attention. A single study conducted in France examined 265,858 births and observed that the frequency of omphalocele tended to increase as maternal education level decreased [99]. In the study, 68.9% of all omphalocele cases occurred among mothers who had less than a high school diploma, followed by 25.8% with a high school diploma, 3.4% for a university degree and 1.7% for completion of technical school [99].

Parity

A small number of studies have examined the relationship between parity and omphalocele [105, 109, 122-124]; although findings were mixed, some studies suggested nulliparity as a risk factor for omphalocele [105, 122-124]. Using NBDPS data, Duong et al. [122] examined maternal parity as an independent risk factor for major birth defects and observed increased odds of nonsyndromic omphalocele among multiparous (aOR= 1.47, 95% CI= 1.01, 2.13) and nulliparous (aOR = 2.33, 95% CI= 1.68, 3.22) mothers compared to primiparous. Contrary to Duong et al., an earlier NBDPS study reported multiparity to have an inverse relationship with omphalocele when compared to primiparity (aOR= 0.44, 95% CI= 0.30, 0.65) [109]; the study

did not examine nulliparity. Another study of nonsyndromic omphalocele from the Texas Birth Defects Registry reported an adjusted prevalence ratio of 1.80 (95% CI= 1.41, 2.30) when comparing nulliparous mothers to those who had one or more previous livebirths [105].

c. Paternal Factors

Age

To date, only two studies have investigated the association between paternal age and omphalocele [125, 126]. One study used linked birth/infant mortality data from 1999-2000, provided by the Centers for Disease Control and Prevention (CDC) and observed an association between younger paternal age (<25) and omphalocele and gastroschisis combined [125]. However, because omphalocele and gastroschisis were analyzed together, estimates may have differed for omphalocele alone. Interaction of paternal and maternal age across all the birth defects was also assessed with no difference in associations for the model that included paternal age only compared to the model that included both paternal and maternal age [125], suggesting that the effect of young paternal age may be explained by maternal risk factors. A more recent study that used NBDPS data for deliveries during 1997-2004 to examine the interaction between maternal and paternal age in predicting omphalocele using a regression plane [126]. The study reported 1) an inverse association with omphalocele for both young maternal and paternal age combined, 2) an association with omphalocele for advanced maternal age and young paternal age combined, and 3) increasing paternal age having a positive association with young maternal age, but, associated with decreasing odds of omphalocele among mothers with advanced maternal age [126].

Race/Ethnicity

To date, there are no known studies that have examined associations between paternal race/ethnicity and omphalocele. However, a small number of studies have controlled for paternal race/ethnicity in an effort to understand the relationship between paternal age and omphalocele [125, 126].

CHAPTER III

METHODS

Case Child Ascertainment and Classification

We examined data from the Iowa Registry for Congenital and Inherited Disorders (IRCID). IRCID is an active, population-based surveillance system that ascertains pregnancies (live births, stillbirths, elective terminations, and spontaneous abortions) diagnosed with a reportable birth defect among Iowa residents. IRCID conducts active surveillance on over 38,000 births annually. Surveillance activities conducted by IRCID are governed by Iowa state law, which specifies that a birth defect is a reportable condition in Iowa [State Legislative Code 641-1.3(139A)]. We obtained data on primary omphalocele diagnosis among live births, fetal deaths (20 weeks gestation or ≥350 grams birth weight), elective terminations, and spontaneous abortions of pregnancies for birth defects for the years 2000-2019. Children diagnosed with omphalocele were coded using the Centers for Disease Control/British Pediatric Association [CDC/BPA] classification codes and classified as definite (diagnosis confirmed by autopsy, surgery, or other postnatal diagnostic method) or probable (i.e. prenatal diagnosis with no postnatal diagnosis). Clinical data for each child with definite or probable omphalocele were reviewed by a clinical geneticist and classified as isolated (no additional, major birth defects), multiple (one or more major birth defects in another organ system), or syndromic (monogenic or chromosomal disorder). For the 235 children with omphalocele ascertained during 2000-2019, 211 were classified as definite, 54 were classified as isolated, 78 as multiple, and 103 as syndromic. We obtained information on selected child, maternal, and paternal characteristics from IRCID.

Iowa Population

We obtained birth and fetal death certificates for all live births and fetal deaths in Iowa for the years 2000-2019 from the Iowa Department of Public Health. Vital records were used to obtain child, maternal, and paternal characteristics for all live and fetal deaths without omphalocele.

Exposure Variables

Child characteristics examined were sex (male, female), year of delivery, plurality (1, ≥2), birth weight (< 2,500, ≥2,500 grams), type of delivery (live birth, fetal death, elective termination, spontaneous abortion), and gestational age (<37, ≥37 weeks). Maternal characteristics examined were age at delivery (<20, 20-34, ≥35 years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), educational attainment at delivery (<12, 12, >12 years), and gravidity (0, ≥1). Paternal characteristics examined included age at delivery (<20, 20-34, ≥35, years), and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other). Among cases, data were available for all children for pregnancy outcome and gestational age and for all mothers for age at delivery and gravidity; for the remaining characteristics, data were available for 93.6% of children for sex, 76.9% for birthweight, 90.2% for maternal race/ethnicity, 72.3% for maternal education, 62.1% for paternal age, and 64.7% for paternal race/ethnicity. Missing data among the Iowa population was less than 1% for all factors except for paternal age (13.1%) and race/ethnicity (15.1%).

Statistical Analysis

Omphalocele prevalence (reported as cases per 10,000 live births and fetal deaths) and 95% CIs were estimated using log-binomial regression models. Prevalence was estimated by child sex, birth year, and maternal race/ethnicity using univariate regression models; annual percentage change in prevalence was estimated in a separate model. Pearson Chi square tests were used to compare distributions of child, maternal, and paternal characteristics among children with

omphalocele and all live births and fetal deaths from 2000-2019. Log-binomial regression models were used to estimate crude and adjusted prevalence ratios (cPR and aPRs, respectively) and 95% CIs for associations between omphalocele and selected child and parental characteristics. Covariates were chosen for the multivariable model based on prior studies or if there was statistical significance ($p<0.05$) from the Chi-square test. Gestational age and birth weight were excluded from the unadjusted analysis because they were not an outcome of omphalocele [116]. Secondary analyses were conducted restricting to definite, isolated, and non-syndromic cases. All analyses were conducted using SAS Software version 9.4 (SAS Institute Inc., 2013). The study was approved by the institutional review boards at the University of Iowa and Emory University.

CHAPTER IV

RESULTS

Overall, 235 omphalocele cases and 781,113 live births and fetal deaths were identified over the twenty-year study period. Of the omphalocele cases, 211 (90%) were definite, 54 (23%) were isolated, 78 (33%) were multiple, and 103 (44%) were syndromic (Table 1). The most common chromosomal syndrome was trisomy 18. Descriptive analyses of infant, maternal, and paternal factors are included in Table 2. Among all cases, 55% of were male and 45% were female. Differences in the distributions for birth weight, gestational age, plurality, and maternal and paternal age differed significantly between children with omphalocele and the Iowa population.

The overall estimated prevalence of omphalocele per 10,000 live births was 3.01 (95% CI = 2.65, 3.42) (Table 3). The estimated prevalence was 3.00 (95% CI = 2.51, 3.59) among males and 2.62 (95% CI = 2.16, 3.19) for females. For maternal race/ethnicity, the prevalence estimate was highest for other race (3.99, 95% CI = 2.32, 6.87) and lowest for Hispanic ethnicity (1.92, 95% CI = 1.09, 3.38). Prevalence of omphalocele in Iowa was highest in 2012 (4.37 per 10,000 live births) and lowest in 2007 (1.95 per 10,000 live births) (Figure 1). The estimated annual percentage change was positive (1.56% per year, 95% CI = -0.69, 3.86) but not statistically significant ($p = 0.17$).

In the unadjusted regression analysis, positive and statistically significant associations were observed between omphalocele and multiple gestation as well as with maternal and paternal ages ≥35 years. Positive but non-significant associations were also observed for male children and other maternal and paternal race/ethnicity, whereas inverse non-significant associations were observed for non-Hispanic Black paternal race/ethnicity and Hispanic maternal and paternal

race/ethnicity. Estimated prevalence ratios for the remaining factors were near the null. Where data permitted, these patterns tended to persist for definite, isolated, and nonsyndromic cases.

Child sex, plurality, maternal age at delivery, and maternal race/ethnicity were included in the multivariable model. Plurality and maternal age at delivery were included due to their significant association with omphalocele, whereas child sex and maternal race/ethnicity were included in the model because they have been widely reported as risk factors in the literature. Paternal age at delivery was excluded due to the proportion of missing data. Results from the multivariable analysis tended to be similar to those from the unadjusted analysis.

CHAPTER V

DISCUSSION

Our population-based, retrospective case-cohort study estimated the prevalence of omphalocele in Iowa from 2000-2019. Prevalence for all case children during this birth period was 3.01 per 10,000 live births. The unadjusted prevalence ratios estimated for our descriptive analysis using data from IRCID from the entire birth period (2000-2019) with complete information on all selected characteristics suggested a higher prevalence of omphalocele among male children, pregnancies with multiple gestation, and those of mothers or fathers aged ≥35 years at delivery. These findings tended to persist in multivariable analyses with the exception of paternal age, which was excluded from the multivariable analysis. Findings restricted to definite, isolated, or nonsyndromic case children tended to be similar to those for all case children.

Our prevalence estimate for omphalocele was higher than the national estimates reported in the three most recent NBDPN studies [9, 10, 50]; however, consistent with one of these NBDPN studies, we did not find a statistically significant trend over the study period [50]. Our finding of a male excess among children with omphalocele supported findings from several previous studies [10, 50, 84, 95, 96, 105, 119, 121], although our estimate was not statistically significant. Similarly, our finding of an increased risk of omphalocele with multiple gestation was consistent with several previous studies [9, 10, 50, 95-102].

Both maternal and paternal age ≥35 years were identified as associated with an increased risk of omphalocele in our unadjusted analysis, which was consistent with previous population-based studies in the US [10, 50, 95, 96, 105, 121] and Australia [84]. The finding for maternal age persisted in adjusted analysis; however, due to missing data, paternal factors were not included in the multivariable models. Unlike previous studies, we did not find an increased risk

of omphalocele among non-Hispanic Black mothers. The population distribution of race/ethnicity in Iowa may have contributed to this finding. Additionally, estimates for maternal education <12 years and >12 years were near the null and not significant, but comparable studies on maternal educational attainment are limited.

Our study has several strengths. It provides the most recent and longest temporal examination of population-based prevalence estimates for omphalocele in the US. Other strengths include use of active case finding approaches and systematic approaches for record abstraction, including data on co-occurring birth defects. Also, clinical data for each case child with omphalocele was reviewed and classified by a clinical geneticist. Additionally, our population data included both live births and fetal deaths.

Our study also had several limitations. IRCID only had data for some of the previously reported risk factors associated with omphalocele. Additionally, there was a high proportion of missingness for paternal factors (~37%) in our study. Nonetheless, more than 90% of data was available for each selected child and maternal characteristics except for maternal educational attainment at delivery (72%). Although multiple gestation has been consistently reported as a risk factor across multiple studies, the etiology is still unclear [10, 109]. Further population-based studies are needed to assess if multiple gestation remains a risk factor across all types of omphalocele (i.e. isolated, multiple, syndromic).

Our study focused on major demographic variables to identify omphalocele prevalence stratified by important infant, maternal, and paternal characteristics. Our analyses supported several previously reported findings, contributing to an increased understanding of selected infant and parental antecedents of omphalocele. Specifically, the findings from our descriptive study suggest that the risk of omphalocele is associated with a plurality of 2 or more and infants

born to mothers ≥ 35 years of age. Future studies with larger sample size should examine prevalence across delivery types such as live births, stillbirths, and terminations and expand the risk factors examined. Additionally, future studies with more complete paternal data should examine the relationship between omphalocele and paternal factors.

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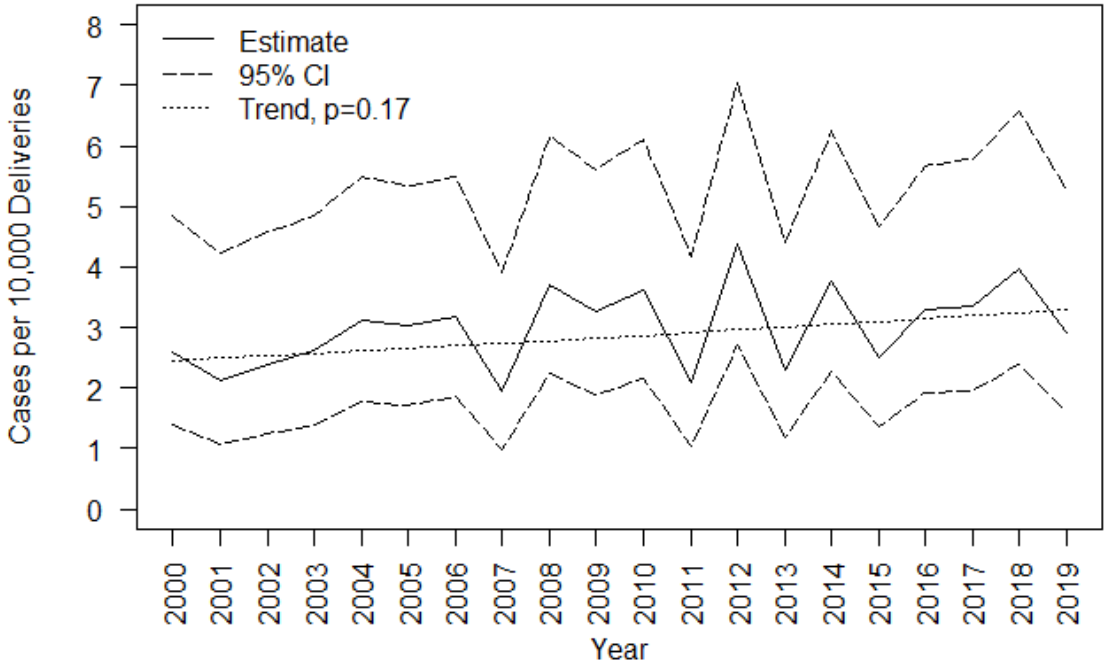

Figure 1. Prevalence of omphalocele in Iowa during 2000-2019

Table 1. Omphalocele phenotype characteristics in Iowa, 2000-2019

Phenotype	**n (%)[a]**
Definite	211 (89.79)
Isolated[b]	54 (22.98)
Multiple[c]	78 (33.19)
MCA	48
MCA / LBWC	10
MCA / OEIS	13
MCA / POC	7
Syndromes	103 (43.83)
Beckwith-Wiedemann Syndrome	16
Turner Syndrome	3
Trisomy 13	32
Trisomy 18	40
Trisomy 21	1
Other Chromosomal Anomaly	11

MCA= multiple congenital anomalies, LBWC= limb-body wall complex, OEIS= omphalocele, cloacal exstrophy, imperforate anus, spinal defect, POC= pentalogy of Cantrell

[a] Percentages may not total 100 due to rounding

[b]No additional major birth defects

[c]One or more major birth defects in another organ system

Table 2. Child, maternal, and paternal characteristics of omphalocele cases and Iowa population, 2000-2019

	All Live Births and Fetal Death	All Omphalocele Cases		Definite	Isolated	Nonsyndromic
	(N=781,113)	(N=235)		(N=211)	(N=54)	(N=132)
Characteristics	**(n%)**	**(n%)**	**p**	**(n%)**	**(n%)**	**(n%)**
Child						
Sex			0.32			
Male	399669 (51.17)	120 (54.55)		112 (55.17)	29 (56.86)	56 (45.90)
Female	381374 (48.83)	100 (45.45)		91 (44.83)	22 (43.14)	66 (54.10)
Missing	70	15		8	3	10
Birth Weight (grams)			<.01			
<2500	55277 (7.08)	100 (55.25)		97 (56.07)	16 (34.78)	55 (50.93)
≥ 2500	725405 (92.92)	81 (44.75)		76 (43.93)	30 (65.22)	53 (49.07)
Missing	431	54		38	8	24
Pregnancy Outcome			NC			
Live Birth	777112 (99.49)	122 (51.91)		122 (57.82)	37 (68.52)	80 (60.61)
Fetal Death	4001 (0.51)	40 (17.02)		32 (15.17)	8 (14.81)	20 (15.15)
Elective Termination	NA	69 (29.36)		56 (26.54)	6 (11.11)	28 (21.21)
Spontaneous Abortion	NA	4 (1.70)		1 (0.46)	3 (5.56)	4 (3.03)
Missing	0	0		0	0	0
Gestational Age (in weeks)			<.01			
<37	76444 (9.80)	165 (70.21)		141 (66.82)	25 (46.30)	83 (62.88)
≥37	703620 (90.20)	70 (29.79)		70 (33.18)	29 (53.70)	49 (37.12)
Missing	1049	0		0	0	0
Plurality			0.006			
1	753864 (96.51)	219 (93.19)		196 (92.89)	50 (92.59)	120 (90.91)

2 or more	27246 (3.49)	16 (6.81)	15 (7.11)	4 (7.41)	12 (9.09)
Missing	3	0	0	0	0
Maternal					
Age at Delivery (years)		<.01[a]			
<20	56468 (7.23)	7 (2.98)	6 (2.84)	0	4 (3.03)
20-34	634573 (81.25)	167 (71.06)	153 (72.51)	43 (79.63)	103 (78.03)
≥35	90002 (11.52)	61 (25.96)	52 (24.64)	11 (20.37)	25 (18.94)
Missing	70	0	0	0	0
Race/Ethnicity		0.32			
Non-Hispanic White	647865 (83.08)	177 (83.49)	161 (83.85)	47 (92.16)	103 (83.06)
Non-Hispanic Black	36943 (4.74)	10 (4.72)	8 (4.17)	1 (1.96)	6 (4.84)
Hispanic	62426 (8.01)	12 (5.66)	11 (5.73)	2 (3.92)	10 (8.06)
Other	32584 (4.18)	13 (6.13)	12 (6.25)	1 (1.96)	5 (4.03)
Missing	1295	23	19	3	8
Education at Delivery (years)		0.99			
<12	103059 (13.25)	22 (13.53)	23 (14.29)	4 (8.89)	14 (13.73)
12	183441 (23.59)	40 (23.53)	38 (23.60)	10 (22.22)	25 (24.51)
>12	491014 (63.15)	107 (62.94)	100 (62.11)	31 (68.89)	63 (61.76)
Missing	3599	65	50	9	30
Gravidity		0.73			
0	240470 (30.82)	70 (29.79)	69 (32.70)	20 (37.04)	47 (35.61)
1+	539800 (69.18)	165 (70.21)	142 (67.30)	34 (62.96)	85 (64.39)
Missing	843	0	0	0	0
Paternal					
Age at Delivery (years)		0.01[a]			
<20	15999 (2.36)	4 (2.74)	4 (2.90)	1 (2.78)	2 (2.33)
20-34	507428 (74.78)	96 (65.75)	92 (66.67)	24 (66.67)	57 (66.28)
≥35	155142 (22.86)	46 (31.51)	42 (30.43)	11 (30.56)	27 (31.40)

Missing	102544	89		73	18	46
Race/Ethnicity			0.26			
Non-Hispanic White	554978 (83.73)	132 (86.84)		125 (87.41)	35 (89.74)	79 (85.87)
Non-Hispanic Black	31164 (4.70)	5 (3.29)		3 (2.10)	0	2 (2.17)
Hispanic	52554 (7.93)	7 (4.61)		7 (4.90)	2 (5.13)	5 (5.43)
Other	24095 (3.64)	8 (5.26)		8 (5.59)	2 (5.13)	6 (6.52)
Missing	118322	83		68	15	40

[a]Chi-square test performed on grouping of ≥35 and <35

Table 3. Prevalence of omphalocele in Iowa, 2000-2019

Characteristics	All Cases (N=235) Prevalence per 10,000 live births and fetal deaths (95% CI)
Overall	3.01 (2.65, 3.42)
Child	
Sex	
Male	3.00 (2.51, 3.59)
Female	2.62 (2.16, 3.19)
Year of Birth	
2000	2.60 (1.40, 4.83)
2001	2.11 (1.06, 4.23)
2002	2.38 (1.24, 4.58)
2003	2.61 (1.40, 4.85)
2004	3.11 (1.77, 5.48)
2005	3.04 (1.73, 5.35)
2006	3.18 (1.85, 5.48)
2007	1.95 (0.97, 3.90)
2008	3.71 (2.24, 6.15)
2009	3.26 (1.89, 5.62)
2010	3.62 (2.14, 6.11)
2011	2.08 (1.04, 4.17)
2012	4.37 (2.72, 7.04)
2013	2.30 (1.20, 4.42)
2014	3.76 (2.27, 6.24)
2015	2.52 (1.36, 4.68)
2016	3.29 (1.91, 5.67)
2017	3.37 (1.95, 5.80)
2018	3.96 (2.39, 6.57)
2019	2.91 (1.61, 5.25)
Maternal	
Race/Ethnicity	
Non-Hispanic White	2.73 (2.36, 3.17)
Non-Hispanic Black	2.71 (1.46, 5,03)
Hispanic	1.92 (1.09, 3.38)
Other	3.99 (2.32, 6.87)

CI, confidence interval

Table 4. Crude analysis of associations between omphalocele and selected child and maternal characteristics among Iowans, 2000-2019

Characteristics	All Omphalocele Cases (N=235) cPR (95% CI)	Definite (N=211) cPR (95% CI)	Isolated (N=54) cPR (95% CI)	Nonsyndromic (N=132) cPR (95% CI)
Child				
Sex				
Male	1.15 (0.88, 1.49)	1.17 (0.89, 1.55)	1.26 (0.72, 2.19)	0.81 (0.57, 1.16)
Female	Referent	Referent	Referent	
Plurality				
1	Referent	Referent	Referent	Referent
2 or more	2.02 (1.22, 3.36)	2.12 (1.25, 3.58)	NC	2.77 (1.53, 5.01)
Maternal				
Age at Delivery (years)				
<35	Referent	Referent	Referent	Referent
≥35	2.69 (2.01, 3.60)	2.51 (1.84, 3.43)	1.96 (1.01, 3.81)	1.79 (1.16, 2.77)
Race/Ethnicity				
Non-Hispanic White	Referent	Referent	Referent	Referent
Non-Hispanic Black	0.99 (0.52, 1.87)	0.87 (0.43, 1.77)	NC	1.02 (0.45, 2.33)
Hispanic	0.70 (0.39, 1.26)	0.71 (0.39, 1.31)	NC	1.01 (0.53, 1.93)
Other	1.46 (0.83, 2.56)	1.48 (0.82, 2.66)	NC	0.97 (0.39, 2.37)
Education at Delivery (years)				
<12	1.02 (0.61, 1.71)	1.08 (0.64, 1.81)	NC	1.00 (0.52, 1.92)
12	Referent	Referent	Referent	Referent
>12	1.00 (0.70, 1.44)	0.98 (0.68, 1.43)	1.16 (0.57, 2.36)	0.94 (0.59, 1.50)
Gravidity				

0	0.95 (0.72, 1.26)	1.09 (0.82, 1.45)	1.32 (0.76, 2.29)	1.24 (0.87, 1.77)
1+	Referent	Referent	Referent	Referent
Paternal				
Age at Delivery (in years)				
<35	Referent	Referent	Referent	Referent
>=35	1.55 (1.09, 2.20)	1.48 (1.03, 2.12)	1.48 (0.73, 3.02)	1.54 (0.98, 2.43)
Race/Ethnicity				
Non-Hispanic White	Referent	Referent	Referent	Referent
Non-Hispanic Black	0.67 (0.28, 1.65)	NC	NC	NC
Hispanic	0.56 (0.26, 1.20)	0.59 (0.28, 1.27)	NC	0.67 (0.27, 1.65)
Other	1.40 (0.68, 2.85)	1.47 (0.72, 3.01)	NC	1.75 (0.76, 4.01)

cPR, crude prevalence ratio; CI, confidence interval; NC, not calculated

Table 5. Adjusted analysis of associations between omphalocele and selected child and maternal characteristics among Iowans, 2000-2019

	All Omphalocele Cases (N=235)	Definite (N=211)	Isolated (N=54)	Nonsyndromic (N=132)
Characteristics	**aPR (95% CI)**	**aPR (95% CI)**	**aPR (95% CI)**	**aPR (95% CI)**
Child				
Sex				
Male	1.19 (0.90, 1.58)	1.20 (0.90, 1.60)	1.23 (0.69, 2.17)	0.86 (0.60, 1.24)
Female	Referent	Referent	Referent	Referent
Plurality				
1	Referent	Referent	Referent	Referent
2 or more	2.09 (1.23, 3.55)	2.10 (1.22, 3.63)	NC	2.83 (1.52, 5.28)
Maternal				
Maternal Age				
<35	Referent	Referent	Referent	Referent
>=35	2.53 (1.84, 3.49)	2.41 (1.72, 3.38)	1.99 (0.99, 4.00)	1.68 (1.05, 2.71)
Race/Ethnicity				
Non-Hispanic White	Referent	Referent	Referent	Referent
Non-Hispanic Black	0.86 (0.42, 1.75)	0.92 (0.45, 1.88)	NC	0.92 (0.37, 2.26)
Hispanic	0.69 (0.38, 1.27)	0.75 (0.40, 1.37)	NC	0.99 (0.50, 1.96)
Other	1.15 (0.61, 2.18)	1.12 (0.57, 2.19)	NC	0.62 (0.20, 1.95)

aPR, adjusted prevalence ratio; CI, confidence interval; NC, not calculated