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Predicting fetal karyotype in fetuses with omphalocele: the current role of ultrasound

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Abstract

Objective—To assess the ability of ultrasound in predicting abnormal karyotype in pregnancies with prenatally diagnosed omphaloceles and to compare its test characteristics to previously published studies.

Methods—A retrospective case-control study of omphaloceles diagnosed at one center was performed from 1995–2007. Cases were those with an abnormal karyotype and controls were those with a normal karyotype. Data collection included demographics, karyotype results, and ultrasound findings. The number and type of associated anomalies were compared between the cases and controls. The sensitivity, specificity, positive predictive value, and negative predictive value for predicting an abnormal karyotype were calculated from previously published studies.

Results—Of the 73 subjects, there were 12 cases and 61 controls. The majority of women were Caucasian and primigravida. The cases were less likely to have an isolated omphalocele [1(8.3%) vs. 27(42.6%), OR 0.122 95% CI 0.02–0.08] but were more likely to have two or more major anomalies [8 (66.7%) vs. 17(27.9%), OR 5.18 95% CI 1.19–24.04] compared to the controls. Cardiac anomalies and only one additional major anomaly were not different between the two groups, $P>0.05$. The test characteristics for this study were similar to previously published studies.

Conclusions—Isolated omphaloceles were more likely to have a normal karyotype; however fetuses with multiple anomalies were more likely to have an abnormal karyotype. Despite advances in ultrasound technology, its ability for predicting an abnormal karyotype in these fetuses has not improved.

Keywords

Prenatal diagnosis; omphalocele; ultrasound

a. Introduction

Omphalocele is a congenital abdominal wall defect that occurs in approximately 1 in 5000 births.^(1, 2) The abdominal contents herniate through the umbilicus and are covered by an amniotic-peritoneal layer. This outpouching may contain bowel, liver, or other abdominal organs.

Chromosomal abnormalities such as trisomy 13 and 18 frequently accompany omphaloceles. Certain prenatal ultrasound characteristics can predict an associated chromosomal abnormality. For example, an intracorporeal liver has a higher association with an abnormal karyotype than an extracorporeal liver.^(3–5) Furthermore, a small defect (<3cm) is more likely to be associated with an abnormal karyotype.⁽⁶⁾ Studies have also shown that the presence of multiple anomalies increases the risk of chromosomal abnormalities.^(3, 6) This information is important because a normal karyotype without major or multiple anomalies can predict neonatal survival approaching 100%.⁽⁷⁾

Historically, clinicians offer invasive genetic testing to women once the diagnosis of omphalocele is made. Although the risks of these procedures, specifically of pregnancy loss, are fairly low, some women may be reluctant to undergo an invasive procedure during pregnancy. De Veciana et al were the first to suggest that antenatal diagnostic procedures may not be warranted with an omphalocele in the setting of otherwise normal fetal anatomy.⁽⁶⁾ This study and most of the studies that guide counseling and management of patients with omphalocele were published more than 10 years ago. Advances in ultrasound technology have been made since that time, including high-resolution imaging and digital signal processing of ultrasounds. If detailed ultrasonography alone can predict the likelihood of an abnormal fetal karyotype, then this information would be beneficial to the provider and the patient when discussing the option of prenatal diagnosis. Patients who are at low risk for chromosomal abnormalities based on ultrasound characteristics may not benefit from invasive testing and therefore avoid its risks. The objective of this study was to evaluate the diagnostic value of modern ultrasound technology in identifying markers of an abnormal karyotype in fetuses with an omphalocele.

b. Materials and Methods

After obtaining approval from the Institutional Review Board, a retrospective chart review of omphaloceles diagnosed by prenatal ultrasound from 1995–2007 at Indiana University-Purdue University Indianapolis (IUPUI) was conducted. Ultrasound models used during this time were ACUSON Sequoia™ 512, Acuson 128XP, and GE Voluson 730 Expert. Omphalocele was defined as a congenital herniation of viscera into the base of the umbilical cord, with a covering membranous sac of peritoneum-amnion.⁽⁸⁾ A keyword search of the prenatal diagnosis ultrasound database at IUPUI identified subjects using the terms “omphalocele”, “abdominal wall defect”, and “umbilical hernia.” Inclusion criteria were a sonographically diagnosed omphalocele at greater than 14 weeks gestational age and available fetal and/or neonatal karyotype results from amniocentesis, chorionic villus sampling, or postnatal/postmortem studies. After careful review of the results from the keyword search, subjects were excluded if another type of abdominal wall defect such as

gastroschisis or umbilical hernia was present. Data collection included demographic information (e.g., maternal age, parity, race), gestational age at diagnosis, ultrasound findings (sac contents, presence of ascites, liver location), fetal echocardiogram, and karyotype. Examples of major malformations included holoprosencephaly, all major cardiac defects including ectopia cordis, cleft lip and palate, amniotic band syndrome, limb-body-wall syndrome, anencephaly, myelomeningocele, clubfeet, clenched fists, macroglossia, ambiguous genitalia, renal agenesis, cystic hygroma, rocker bottom feet, and diaphragmatic hernia. Soft markers (pyelectasis, intracardiac echogenic focus, ventriculomegaly, echogenic bowel, thick nuchal fold, single umbilical artery, and shortened long bones) associated with aneuploidy were also reviewed. A separate cytogenetics database confirmed the karyotypes and an abnormal karyotype was defined as one known to be phenotypically significant. Neonatal records were reviewed to ensure postnatal confirmation of the diagnosis.

The number and type of associated congenital defects was compared between those with abnormal (cases) and normal (controls) karyotypes. Statistical analysis included the chi-square and Fisher's exact tests for categorical data and the student's t-test for continuous data. Odds ratios (OR) with 95% confidence intervals (CI) were reported. P values less than 0.05 were considered statistically significant. A logistic regression analysis controlled for variables (e.g., maternal age, gestational age at diagnosis, type of associated anomaly, and male sex) that could potentially influence karyotype in fetuses with omphaloceles. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated for five studies (^{3, 6, 9-11}) that reported the presence of associated malformations in prenatally diagnosed omphaloceles as predictive of an abnormal karyotype. The same was done with the data from the current study and the results were compared.

c. Results

Of the 162 fetuses with anterior abdominal wall defects identified in the keyword search, 78 were not omphaloceles or had missing data and 12 had an unknown karyotype. A total of 73 met the inclusion criteria. Of these, 12 (16%) had an abnormal karyotype (cases) and 61 (83%) had a normal karyotype (controls). There was no statistical difference in the mean age, race, number of primigravid patients, or gestational age at diagnosis between the two groups (Table 1), but the cases were more likely to be over 35 years old compared to the control group; 3(25%) vs. 4(6.6%), OR 9.67, 95% CI 2.0–46.7.

The most common source for karyotyping was amniocentesis (76.6%), followed by neonatal blood (11%), post delivery tissue such as placenta or an autopsy (9.6%), and chorionic villus sampling (2.7%). Of the abnormal karyotypes, trisomy 18 (n=8) was the most common followed by single cases of trisomy 13, triploidy, trisomy 2 mosaic, and 46,XX,del(5)(q13q22) mosaic. There was no difference in fetal sex between the two groups; however among those fetuses with trisomy 18, there was a male to female ratio of 3:1.

In the entire group, there were three amniotic band syndromes, five Pentalogy of Cantrell, and one presumed Beckwith-Weidemann syndrome diagnosed prenatally. The most common associated anomalies were cardiac, central nervous system, and skeletal defects. The cases

were less likely to have an isolated omphalocele compared to the controls [1(8.3%) vs. 27(42.6%), OR 0.122 95% CI 0.02–0.08] (Table 2). The cases had a higher occurrence of skeletal (i.e. kyphoscoliosis, club feet, absent limb) and central nervous system anomalies (i.e. holoprosencephaly, microcephaly, neural tube defects). They were also more likely to have two or more associated major anomalies compared to the controls. In the regression analysis, the relationship between a non-isolated omphalocele and an abnormal karyotype was greater (OR 20.2, 95% CI 1.8–23) after controlling for maternal age, gestational age at diagnosis, the type of associated anomalies, and male sex. In addition, the risk for an abnormal karyotype increased by 14% for every year increase in maternal age (OR 1.14, 95% CI 1.01–1.29).

The liver location and the presence of ascites were documented in 56 and 54 of the fetal ultrasounds, respectively. There was no difference in the sac contents between the two groups. In total, an extracorporeal liver was identified in 45/56 (80.4%) with 3 (75%) cases and 42 (80.8%) controls ($P=0.99$). Ascites was present in 9/54 (16.7%) total subjects with 1 (25%) case and 8 (16%) controls ($P=0.529$).

The sensitivity, specificity, positive predictive value, and negative predictive value of associated malformations in predicting an abnormal karyotype between our study and those previously published were similar (Table 3).

d. Discussion

In this case-control study of 73 prenatally diagnosed omphaloceles, fetuses with abnormal karyotypes were more likely than those with a normal karyotype to have two or more associated major anomalies. Skeletal and central nervous system anomalies were found more frequently in those fetuses with abnormal karyotypes. The positive association between additional major malformations and an abnormal karyotype has been previously published^(3, 6). Despite advances in ultrasound technology, its predictive value in diagnosing karyotypic abnormalities in fetuses with omphalocele has not changed significantly in the last 10 years. Overwhelmingly, the presence of associated anomalies has a high sensitivity for an abnormal karyotype and if this finding is absent, the likelihood that the karyotype will be normal is at least 90%. The lack of improvement in its predictive power is likely because associated major anomalies are usually apparent enough to be seen at almost any ultrasound resolution.

There are two limitations to our study. The first is the small sample size. Our proportion of fetuses with an abnormal karyotype was 16%. Aneuploidy occurs in 10–49% of omphaloceles which is similar to our findings but the lower occurrence of aneuploidy in general in this prenatal database may result from our exclusion of subjects without a karyotype ($n=12$). These women may have decided to terminate the pregnancy solely based on other associated anomalies. Availability of these karyotypes may have increased the proportion of aneuploid fetuses in our study. The second limitation is the unavailability of the all ultrasound images for review. Several investigators have examined the size of the herniation and its contents (liver, ascites, etc.) with the intent of predicting an abnormal

karyotype.^(3–6, 12, 13) These associations were not seen in our case control study which was likely due to underreporting of the specific sac contents and characteristics.

The presence of an omphalocele on prenatal sonogram should alert the clinician of the increased risk for fetal aneuploidy. Genetic counseling and fetal karyotyping continues to be the recommendation; however, patients will always be hesitant about the risks of invasive testing. Currently, the advent of cell free fetal DNA (cfDNA) testing in maternal serum is making noninvasive prenatal diagnosis a reality. No studies to date have reported its utility in cases of omphalocele, but with detection rates of 97–100% for trisomy 18^(14, 15), the most common chromosomal abnormality in omphaloceles, this test could be useful. However, given the limitations of cfDNA testing at this time, invasive genetic testing that obtains a complete karyotype in the setting of an anomaly remains the standard. Microarray testing for deletions and duplications is also recommended in the setting of congenital anomalies as this can provide additional clinically significant genetic information in 6% of these patients⁽¹⁶⁾.

Ultrasound can be a useful predictor of aneuploidy in cases with omphalocele. Our case control study, along with previously published studies, demonstrated that the presence of additional anomalies increased the likelihood of an abnormal karyotype. Specifically, we showed that increasing maternal age, skeletal and central nervous system anomalies, and two or more associated malformations increases the likelihood of an abnormal karyotype in fetuses with an omphalocele. Conversely, an isolated omphalocele can provide some reassurance regarding a normal karyotype. This information can be used when counseling women regarding the importance of invasive testing, as aneuploidy and/or multiple anomalies are associated with poor neonatal outcomes.

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Table 1

Participant Demographics

Variable	Total n=73	Abnormal Karyotype n=12	Normal Karyotype n=61	P value, OR (95% CI)
Age (yrs)				
Mean, SD, range	25.7±6.8 (15–45)	28±8.9	25.2±6.3	0.200
>35 years (n,%)	7 (9.6)	3 (25.0)	4 (6.6)	0.012, OR 9.67 (2.01–46.7)
Race (n,%)				
Caucasian	64 (87.8)	10 (83.3)	54 (88.5)	0.613
African American	4 (5.5)	1 (8.3)	3 (4.9)	
Hispanic	4 (5.5)	1 (8.3)	3 (4.9)	
Unknown	1 (1.4)		1 (1.6)	
Primigravidas (n,%)	30 (46.8) n=64*	4 (57.1)	26 (45.6)	0.697
Gestational age at diagnosis (Mean ± SD, range)	21.7±5.8 (13–36)	21.6±6.3	21.7±5.8	0.920

* Gravidity was only documented for 64 women.

Table 2

Associated anomalies of fetuses with normal and abnormal karyotypes

Associated Anomalies	Total N=73 (n,%)	Abnormal Karyotype n=12 (n,%)	Normal Karyotype n=61 (n,%)	P value, OR (95% CI)
None	27 (37.0)	1 (8.3)	26 (42.6)	0.026, OR 0.12 (0.02–0.08)
Cardiac anomaly only	17 (23.3)	4 (33.3)	13 (21.3)	0.456
Musculoskeletal anomaly only	22 (30.1)	8 (66.7)	14 (23.0)	0.005, OR 6.71 (1.84–24.26)
Central nervous system only	17 (23.3)	6 (50.0)	11 (18.0)	0.026, OR 4.55 (1.04–20.40)
>1 Major anomaly	25 (34.2)	8 (66.7)	17 (27.9)	0.017, OR 5.18 (1.19–24.04)
Major anomaly and soft marker*	5 (6.9)	1 (8.3)	4 (6.6)	1.000
Soft marker* only	6 (8.2)	1 (8.3)	5 (8.2)	1.000

* soft markers: choroid plexus cysts, pyelectasis, single umbilical artery

Summary of previous studies of the predictive value of associated anomalies on ultrasound to predict aneuploidy in fetuses with omphaloceles

Table 3

Author, year	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Total number of cases
Gilbert ⁹ , 1987	93.3%	53.3%	66.7%	88.9%	30
Nyberg ³ , 1989	60.0%	81.3%	66.7%	76.6%	26
Nicolaides ¹¹ , 1992	97.6%	37.8%	47.1%	96.6%	116
De Veciana ⁶ , 1994	100%	77.4%	56.3%	100%	40
Axt ¹⁰ , 1999	100%	42.1%	38.8%	100%	26
Our study	91.8%	42.6%	23.9%	96.3%	73