Received: 2 October 2022 | Revised: 12 December 2022 | Accepted: 2 January 2023

DOI: 10.1002/pd.6302

ORIGINAL ARTICLE

PRENATAL DIAGNOSIS WILEY

Turner syndrome-omphalocele association: Incidence, karyotype, phenotype and fetal outcome

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Abstract

Objective: Omphalocele is known to be associated with genetic anomalies like trisomy 13, 18 and Beckwith–Wiedemann syndrome, but not with Turner syndrome (TS). Our aim was to assess the incidence of omphalocele in fetuses with TS, the phenotype of this association with other anomalies, their karyotype, and the fetal outcomes.

Method: Retrospective multicenter study of fetuses with confirmed diagnosis of TS. Data were extracted from a detailed questionnaire sent to specialists in prenatal ultrasound.

Results: 680 fetuses with TS were included in this analysis. Incidence of small omphalocele in fetuses diagnosed ≥12 weeks was 3.1%. Including fetuses diagnosed before 12 weeks, it was 5.1%. 97.1% (34/35) of the affected fetuses had one or more associated anomalies including increased nuchal translucency (≥3 mm) and/or cystic hygroma (94.3%), hydrops/skin edema (71.1%), and cardiac anomalies (40%). The karyotype was 45,X in all fetuses. Fetal outcomes were poor with only 1 fetus born alive.

Conclusion: TS with 45,X karyotype but not with X chromosome variants is associated with small omphalocele. Most of these fetuses have associated anomalies and a poor prognosis. Our data suggest an association of TS with omphalocele, which is evident from the first trimester.

Key points

What are the novel findings of this work?

- Omphalocele is known to be associated with chromosomal anomalies, mostly Trisomy 13, 18 and Beckwith–Wiedemann syndrome. The association with Turner syndrome has been described only sporadically.

What are the clinical implications of this work?

- We report a significant incidence of omphalocele in prenatally diagnosed fetuses with Turner syndrome and a 45,X karyotype

1 | INTRODUCTION

Omphalocele is a midline abdominal wall defect that occurs during the embryonic period. The incidence of omphalocele at 11–14 weeks of gestational age (GA) is between 11 and 23:10,000.[1,2] At birth, it is approximately 2:10,000.[3–7] Omphalocele seems to be due to a primary failure of the lateral ventral folds, which form the primitive umbilical ring and an incomplete migration and differentiation of the mesodermal somites.[3,8–10] Since midgut herniation remains a physiological finding up to the 12th week of gestation, this is a differential diagnosis and isolated omphalocele cannot be reliably diagnosed on prenatal ultrasound until after 12 weeks.[5,11–17] Large giant (>5 cm) omphalocele usually contain liver, have a lower risk of genetic anomalies but are frequently associated with pulmonary hypoplasia.[5,18] In comparison, small omphalocele (<5 cm) usually contain only bowel and are frequently associated with chromosomal disorders, mainly trisomy 13 and 18.[5,18,19] Omphalocele is mainly a non-isolated malformation and associated anomalies and/or genetic disorders are found prenatally in 41%–69% of fetuses and often determine the fetal outcome in these pregnancies.[2,17,20] Omphalocele can be part of a multi-malformative sequence like OEIS (Omphalocele, Exstrophy, Imperforate anus, Spinal defect) and Pentalogy of Cantrell or syndromes such as Beckwith–Wiedemann syndrome, Donnai–Barrow syndrome, or Shprintzen–Goldberg omphalocele syndrome.[5,21–23] X-linked inheritance has been described.[5] Few studies and case reports have described fetuses with Turner syndrome and predominantly small omphalocele containing only bowel.[2,24–27]

Turner syndrome is a chromosomal anomaly due to a complete or partial absence or a structural anomaly of the second X-chromosome in a female. Affected fetuses have a high risk of

miscarriage and intrauterine fetal demise (IUFD), which is more pronounced with the karyotype 45,X, and if fetal hydrops is present.[28–30] The karyotype 45,X is more frequent in the prenatal series.[28,31,32] Mosaic forms tend to have milder manifestations and fetal hydrops is less frequent.[33] There is a huge phenotypic variability and the association between karyotype and phenotype cannot always be predicted. Recent evidence suggests that the karyotype–phenotype relation cannot be explained by the gene dosage alone and epigenetic mechanisms may influence autosomal gene expression.[34,35] The prenatal phenotype includes fetal hydrops, cystic hygroma, congenital heart defects primarily affecting the left outflow tract and the pulmonary venous return, kidney anomalies, intrauterine growth restriction (IUGR), and edema of the hands and feet.[36–39] Omphalocele has not yet been reported as a typical feature in fetuses with Turner syndrome.

Our study aimed to estimate the incidence of omphalocele in fetuses with Turner syndrome, its association with other anomalies, the karyotype of affected fetuses, and the fetal outcome.

2 | METHOD

2.1 | Study design

We designed a retrospective multicenter study in Germany. This study was approved by the ethic committee of the Justus-Liebig-University, Gießen, Germany, AZ 119/19.

Our Inclusion criteria were:

1. Prenatally suspected or diagnosed fetuses with Turner syndrome between 2000 and 2021
2. Confirmed karyotype of Turner syndrome by prenatal chorionic villous sampling (CVS) and/or amniocentesis (AC) or postnatal karyotyping on blood.
3. Available fetal ultrasound data

Exclusion criteria were fetuses with suspected Turner syndrome by prenatal screening without genetic confirmation.

Data were acquired anonymously through a detailed questionnaire sent electronically to referral centers for fetal medicine in Germany (Level II and III according to the German Society for Ultrasound in Medicine, DEGUM) between September 2019 and May 2021. The reasons for referral were maternal request/advanced maternal age, combined first trimester screening (cFTS), abnormal screening results (cFTS and cfDNA), and abnormal findings on prenatal ultrasound. The questionnaire consisted of 24 questions divided into maternal demographic characteristics, ultrasound abnormalities, specific karyotype, complications during pregnancy, outcome, and characteristics of the children after birth (SupplementaryInformation S1). As omphalocele was not suspected to be associated with Turner syndrome, we did not specially ask for this malformation, but specialists added this finding to question number 19 in the questionnaire. This multicenter database has also been used as source for another publication with a different focus on fetuses with Turner syndrome and the corresponding pregnancy outcome.[33]

2.2 | Outcome measures

We focused on the presence of omphalocele in a prenatally diagnosed population of fetuses with Turner syndrome. We analyzed the gestational age at diagnosis, the specific karyotype, associated anomalies, and pregnancy outcomes.

Karyotype analysis: we have differentiated two groups, karyotype 45,X (monosomy X) and X-chromosome variants. X chromosome variants include X chromosome mosaics (45,X/46,XX, 45,X/46XY with female phenotype and 45,X/47,XXX), structural anomalies of the second X chromosome, and unbalanced X-autosome translocations.

In addition, we carried out a group comparison between cases with Turner syndrome and omphalocele (n = 35) versus cases with Turner syndrome and the karyotype 45,X without omphalocele (n = 574). Fetuses with an X chromosome variant were excluded because none of these had an omphalocele and the outcome in general is expected to be more favorable than in cases of monosomy X.

The groups were compared regarding the continuous variables maternal age (MA), gestational age at diagnosis (GA), body mass index (BMI), crown-rump length (CRL), and the categorical variables fetal hydrops/generalized skin edema (FH), cystic hygroma/increased NT (CH), cardiac anomaly (CA), renal anomaly (RA), mode of conception, and pregnancy outcome.

Increased nuchal translucency (NT) in the first trimester was defined as NT ≥ 3 mm and cystic hygroma was defined as fluid-filled septated sacs in the posterior occipital region of the fetus.[40]

2.3 | Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows®, version 26.

The continuous variables were analyzed using t-tests (with Cohen's d as the standardized effect size measure) with the exception of variable GA: because of severe outliers, GA was analyzed using Mann–Whitney tests (with r as the standardized effect size measure). All continuous variables were described using means, standard deviations, and minimum/maximum.

The categorical variables were analyzed using Chi-squared tests. In 2-by-2 tables, Chi^2 N-1 tests are reported, and in larger tables, Pearson's Chi^2 tests. These comparisons are accompanied with Cramér's V as the standardized effect size measure.

A p-value <0,05 was accepted as statistically significant.

Interpretation of effect size measures:

r and V: 0.1 = weak; 0.3 = medium; 0.5 = strong association.

d: 0.2 = weak; 0.5 = medium; 0.8 = strong association.

3 | RESULTS

3.1 | Data collection

Eighteen referral centers participated in the survey and provided data for 733 patients until August 2021. Of these, 53 were excluded because Turner syndrome could not be confirmed, or karyotype was not available. 680 pregnancies fulfilled our inclusion criteria and were analyzed in this study. In 83% (565/680), the outcome was available. Mean gestational age at diagnosis of Turner syndrome was 13.7 weeks. In 29/680 cases, the gestational age at diagnosis was not documented in the questionnaire. 455/651 (69.9%) pregnant women had a documented expert scan (Level II and III according to the German Society for Ultrasound in Medicine, DEGUM) at a referral center in the first trimester before 14 weeks.

3.2 | Estimated incidence of omphaloceles in fetuses with Turner syndrome

An omphalocele was detected using prenatal ultrasound in 35/680 (5.1%) fetuses. In only one fetus, omphalocele was an isolated finding. Excluding cases that were only scanned before 12 weeks, the percentage was 3.1%.

Mean gestational age at diagnosis for cases with omphalocele was 12.6 weeks and was documented in 34/35 cases. In the one case with no documentation of GA at diagnosis, CRL was 44.7 mm, and we therefore suppose that GA was <12 weeks. One pregnant woman in this group presented for an expert scan at the referral center at 25 weeks, and we do not have further information on the first trimester ultrasound.

The characteristics of the affected pregnancies are shown in Table 1.

3.3 | Association of fetuses with Turner syndrome and omphaloceles with other anomalies

97.1% (34/35) of fetuses with omphalocele showed one or more associated anomalies. These included increased nuchal translucency (NT) ≥3 mm and/or cystic hygroma (94.3%), hydrops/skin edema (77.1%), and cardiac anomalies (40%). Cardiac anomalies were VSD/AVSD in 5/35, AVSD with coarctation of the aorta in one case, hypoplastic left heart in 3/35, coarctation of the aorta in 1/35, and pulmonary insufficiency in 1/35 (at 25 weeks GA). In 3 cases, the type of cardiac anomalies was not further specified. Other associated findings were kidney anomalies (2.9%), dorsal edema of the hands and feet (2.9%), single umbilical artery (SUA) (14.3%), umbilical cord cyst (5.7%), IUGR (8.6%), and hypoplastic nasal bone (2.9%).

25/35 omphaloceles were described as small, containing only bowel; in 10 cases, further information on the type of omphalocele was not provided.

TABLE 1 Characteristics of the affected pregnancies

Characteristic (valid *n*) (Total *n* = 35)	Mean (min-max) or *n* (%)
Maternal characteristics	
Age (years) (*n* = 34)	28.8 (19–36)
BMI (*n* = 32)	24.4 (18.5–42.2)
Mode of conception (*n* = 33)	
Spontaneous conception	29 (87.9)
IVF/ICSI	4 (12.1)
GA at diagnosis (*n* = 34)	
11 + 0 to 11 + 6 weeks	13 (38.2)
12 + 0 to 12 + 6 weeks	15 (44.1)
13 + 0 or later	6 (17,6)
CRL (mm) (*n* = 26)	56.7 (43–84)
NT/Cystic hygroma (mm) (*n* = 26)	8.5 (5.2–15.7)

Abbreviations: BMI, body mass index; CRL, Crown–rump length; GA, gestational age; ICSI, Intracytoplasmatic sperm injection; IVF, in-vitro fertilization; NT, nuchal translucency.

3.4 | Karyotype of fetuses with Turner syndrome and omphalocele

All fetuses with omphalocele had the karyotype 45,X (monosomy X). No X chromosome variant was detected. Diagnosis was made in all but one case by chorionic villous sampling (CVS) in the first trimester. In one case, karyotype was done on amniotic fluid in a fetus first diagnosed at 25 weeks. 71/680 (10.4%) fetuses had an X-chromosome variant. Omphalocele was not present in any of these. Fetal hydrops/generalized skin edema was seen in 11.3%, cystic hygroma/increased NT was seen in 28.2%, cardiac anomalies in 19.7%, and renal anomalies in 2.8% of these fetuses.

3.5 | Outcome of fetuses with Turner syndrome and omphalocele

Outcome data were available for 33/35 pregnancies. In 25/33 cases the pregnancy was terminated in the first or early second trimester. Selective feticide of the affected twin was performed in two diamniotic dichorionic (DA/DC) twin pregnancies, conceived with intracytoplasmatic sperm injection (ICSI). The second most common outcome was spontaneous abortion (6/33) or intrauterine fetal demise (IUFD) (1/33). One fetus was born alive.

Two pregnancies continued pass 24 weeks. One pregnant woman presented for the first time at the specialist center at 25 weeks. We do not have information if a first trimester scan was done with the local provider. Additional findings on ultrasound were an umbilical cord cyst, dorsal edema of the feet, and pulmonary insufficiency. This fetus died during pregnancy. The second baby was born alive. The omphalocele contained only bowel and was diagnosed in the first trimester. Additional ultrasound anomalies were increased NT and generalized skin

edema that resolved after the first trimester (Figure 1). A small ventricular septal defect (VSD) was first suspected but could not be confirmed. The baby was spontaneously delivered at 38 weeks GA with a weight of 2630 gr (<5th percentile) and length of 46 cm (<5th percentile). The newborn had edema of the hands and feet and hyperconvex nails of the feet (Figure 2). Surgery was successfully performed within 24 h of life and consisted of primary repair.

Outcome in fetuses with an X-chromosome variant was more favorable with 54.4% of fetuses born alive, 8.8% miscarriage/IUFD, and 36.8% TOP.

3.6 | Comparison of fetuses with Turner syndrome and the karyotype 45,X with and without omphalocele

When comparing 2 groups of fetuses with karyotype 45,X with and without omphalocele, there were only 2 significant differences with weak effect size: Gestational age at diagnosis, which was higher in the group without omphalocele (12.6 vs. 13.6 weeks), and cystic hygroma/increased NT, which was significantly less frequent in the group without omphalocele. All other parameters did not show any significant difference (Table 2).

4 | DISCUSSION

Whilst omphalocele has been reported in Turner syndrome, it has never been considered a true association.[2,24,25,27,41] In our analysis of 680 fetuses with confirmed Turner syndrome, 5.1% had an omphalocele. When excluding cases that were scanned exclusively before 12 weeks, the incidence was 3.1%. All affected fetuses had the karyotype 45,X and most fetuses also had associated anomalies with cystic hygroma, fetal hydrops/generalized edema, and

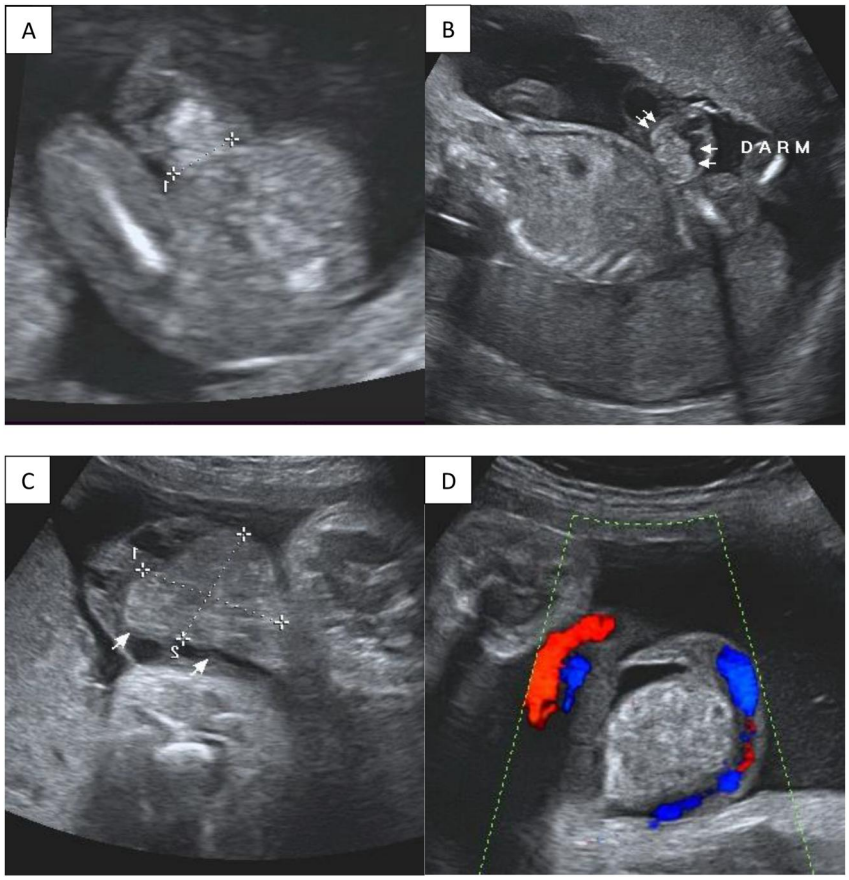

FIGURE 1 ((A)–(D)) serial prenatal ultrasound of a small bowel containing omphalocele. (A) 14 + 5 weeks, (B) 18 + 4 weeks GA, ((C), (D)) 35 + 4 weeks (copyright Dr. Gloning, Pränatal-Medizin München) [Colour figure can be viewed at wileyonlinelibrary.com]

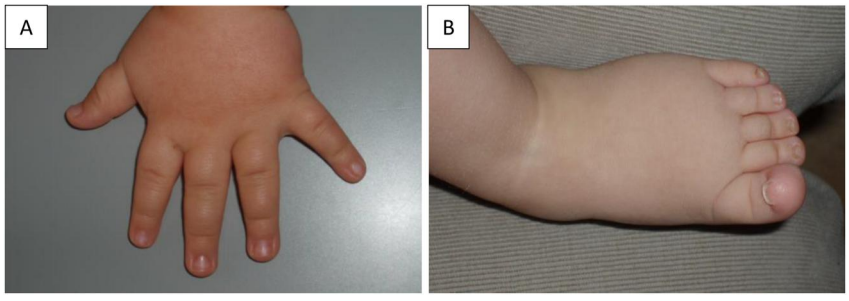

FIGURE 2 ((A), (B)) neonatal phenotype with edema of the hands and feet and hyperconvex nails: (copyright Dr. Gloning, Pränatal-Medizin München) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Comparison of fetuses with karyotype 45,X with and without omphalocele

	Turner syndrome with omphalocele (n = 35)	Turner syndrome without omphalocele and karyotype 45,X (n = 574)	p comparison omphalocele/no omphalocele and karyotype 45,X (ES)
Maternal characteristics Mean/SD, (min-max) (Valid n)			
Age (years)	28.8; 5.2; (19–36)	30.4; 5.2; (16–45)	0.093[a]
	(n = 34)	(n = 567)	(d = 0.14)
BMI	24.4; 5.3; (18.5–42.2)	24.3; 4.5; (16.4–40.8)	0.911[a]
Valid (n)	(n = 32)	(n = 534)	(d = 0.01)
Mode of conception (valid n)	n = 33	n = 523	0.091[c] (V = 0.07)
Spontaneous n (%)	29 (87.9)	496 (94.8)	
IVF/ICSI n (%)	4 (12.1)	27 (5.1)	
GA at diagnosis Mean/SD, (min-max) (Valid n)	12.6; 2.4; (11–25) (n = 34)	13.6; 2.5; (9.1–25.5) (n = 554)	<0.001[b] (r = 0.14)
Associated anomalies n (%)			
Fetal hydrops/generalized skin edema	27 (77.1)	376 (65.5)	0.158[c] (V = 0.057)
Cystic hygroma/increased NT	33 (94.3)	451 (78.6)	0.026[c] (V = 0.091)
Cardiac anomalies	14 (40)	214 (37.3)	0.747[c] (V = 0.013)
Renal anomalies	1 (2.9)	30 (5.2)	0.536[c] (V = 0.025)
Outcome n (%)			
Miscarriage/IUFD	7 (21.2)	97 (20.4)	0.913[c]
	(n = 33)	(n = 475)	(V = 0.01)
TOP	25 (75.8)	329 (69.3)	0.414[c]
	(n = 33)	(n = 475)	(V = 0.04)
LB	1 (3)	49 (10.3)	0.235[d]
	(n = 33)	(n = 475)	(V = 0.06)

Abbreviations: BMI, body mass index; ES, Effect size measure; ICSI, intracytoplasmatic sperm Injection; IUFD, intrauterine fetal demise; IVF, in-vitro fertilization; LB, live birth; max, maximum; min, minimum; NT, nuchal translucency; SD, standard deviation; TOP, termination of pregnancy.

[a]t-Test.

[b]Mann–Whitney Test.

[c]Chi^2 N-1-Test.

[d]Fisher's Exact Test.

cardiac anomalies being most frequent. Survival was poor, and most pregnancies were terminated, or fetuses died spontaneously. Comparison of fetuses with karyotype 45,X with and without omphalocele showed two significant differences, however with a weak effect size: gestational age at diagnosis and the presence of cystic hygroma/increased NT. Mean gestational age at diagnosis was higher in the group without omphalocele (12.6 vs. 13.6 weeks); however, both were ≥12 weeks GA. Cystic hygroma/increased NT was more frequent in the group with omphalocele. Outcome was not different in both groups and seems to be determined more by the 45,X karyotype than by the presence of the omphalocele.

4.1 | Comparison with the literature

Omphalocele is currently not considered a typical finding of Turner syndrome, but the incidence of omphalocele in prenatally diagnosed cases of Turner syndrome has never been assessed.[36–39] Govaerts et al. in 1997 raised the question about coincidence or association.[26] Previous studies have focused on the percentage of Turner syndrome in fetuses with omphalocele in comparison to other chromosomal disorders. In this context, Turner syndrome has been found in 6.6%–8.1% of fetuses with omphalocele.[2,24]

Anomalies in fetuses with Turner syndrome detectable on prenatal ultrasound include fetal hydrops, cystic hygroma, congenital

heart defects primarily affecting the left outflow tract and the pulmonary venous return, kidney anomalies, agenesis of ductus venosus, intrauterine growth restriction (IUGR), and edema of the hands and feet.[36–39] Few studies and case reports ($n = 4$) report on omphalocele in fetuses with Turner syndrome.[2,24–27,41] Consistent with our results, Kagan et al. and Syngelaki et al. found predominantly small, only bowel-containing omphaloceles in fetuses with Turner syndrome at 11–14 weeks.[2,24] In Turner syndrome, omphalocele is usually associated with other anomalies.[26,27,41] In comparison to isolated, "physiologic" gut herniation in a fetus with normal karyotype, non-isolated omphaloceles are less frequently expected to resolve with advancing gestational age when diagnosed between 11 and 12 weeks.[15–17] We therefore included all fetuses with omphalocele, also the ones diagnosed between 11 and 12 weeks, but agree with the importance of follow-up ultrasound in these fetuses if the finding is isolated.

Different karyotypes can lead to Turner syndrome, including monosomy X, as well as mosaics and unbalanced structural anomalies of the second X chromosome. The phenotype cannot be fully predicted by the karyotype. Prenatally 45,X karyotype is more prevalent than after birth and in comparison to mosaics more often associated with a severe phenotype, and poor outcome.[28,31,37,42] In our study, all fetuses with omphalocele and Turner syndrome had the karyotype 45,X (monosomy X). No fetus with an X chromosome variant showed this feature. This is consistent with the four other published reports with Turner syndrome-omphalocele association.[25–27,41] A potential mechanism is currently unknown. Toriello and Higgins have raised the question of X-linked midline defects.[43]

Several recent studies have shown that in adults with TS, the methylome and transcriptome of blood is altered globally and in addition, new data also points to pervasive alterations in non-coding RNA expression, such as circular RNA and probably also micro RNA in blood, muscle, and fat.[34,35,44–48] Jointly, these papers point to several different pathways and regulatory functions that are changed in TS. How such changes would impact the developing TS fetus is not yet clear, but it is an alluring thought that we might soon understand much more about the genomics of TS and how this impacts the phenotype.

The outcome in fetuses with Turner syndrome is guarded. Prenatal mortality is high, especially but not exclusively in the group with increased NT and fetal hydrops.[28] This is due to spontaneous miscarriage and high rate of termination of pregnancy, particularly in the group with karyotype 45,X.[31,42,49–51] Reasons associated with TOP and fetal loss in addition to the fetal karyotype are increased NT and associated fetal anomalies.[51] Our study supports these findings independent of the presence of fetal omphalocele. In the group with an X chromosome variant, the outcome is better with a live birth rate of 54.4%, an IUFD rate of 8.8%, and TOP in 36.8%.

4.2 | Clinical and research implications

In fetuses with omphalocele, Turner syndrome should be considered a possible underlying condition. This is especially true when other typical anomalies such as cystic hygroma or generalized edema/fetal hydrops are found on prenatal ultrasound.

Based on our findings and the literature, the karyotype of these fetuses is predominantly 45,X. To the best of our knowledge, the exact mechanism causing omphalocele in Turner syndrome is unknown and could be the subject of further research, including epigenetic factors as reason for Turner phenotype.

4.3 | Strengths and limitations

An important limitation of this study is its retrospective design increasing the risk for information bias. Moreover, our questionnaire—primarily focusing on Turner syndrome—did not purposefully include omphalocele as an associated malformation. It was added by the specialists in a field referred to as other prenatal anomalies. We are aware that cases might have been missed and that we therefore may have underestimated the true incidence of this association. In addition to this inclusion bias, we also had a reporting bias due to incomplete filling of the questionnaire. In most cases, we do not have detailed documentation of follow-up ultrasound after the first trimester and can therefore not comment on further persistence of the omphalocele. We acknowledge this limitation and have therefore reported the incidence separated for of all cases and cases diagnosed ≥12 weeks. However, omphalocele in non-isolated aneuploid fetuses, such as those in our cohort, are less likely to regress after diagnosis in the first trimester.[15–17] As most pregnancies were terminated in late first or early second trimester and autopsy was not performed, we cannot make any statement regarding the natural history.

Our study also has numerous strengths. To the best of our knowledge, this is the largest study describing the incidence of fetuses with Turner syndrome-omphalocele association. It was a multicenter study collecting data from experts in fetal medicine lowering the risk for reporting and analysis biases. Moreover, we reported more in detail about the specific karyotype, taking into consideration the variety of karyotypes leading to the phenotype of Turner syndrome.

5 | CONCLUSION

As a summary, we conclude that in fetuses with Turner syndrome and the karyotype 45,X diagnosed prenatally, there is a small but significant number of small omphalocele, containing only bowel. This does not appear to occur in fetuses with X chromosome variants. For cases diagnosed at or after 12 weeks, the incidence in the cohort we have ascertained was 3.1% and suggests that omphaloceles could be considered as part of the prenatal Turner syndrome phenotype. Most fetuses with this association have associated anomalies such as fetal hydrops, skin edema, cystic hygroma, and cardiac defects, and the pregnancy outcome is poor.

ACKNOWLEDGMENT

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the ethic committee of the Justus-Liebig-University, Gießen, Germany, AZ 119/19.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bedei I, Gloning K-P, Joyeux L, et al. Turner syndrome-omphalocele association: incidence, karyotype, phenotype and fetal outcome. *Prenat Diagn*. 2023;43(2):183-191. https://doi.org/10.1002/pd.6302