

Adverse Perinatal Outcomes Associated with True Knot of the Umbilical Cord: A Multicenter Retrospective Study

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Abstract

Objective This study aimed to estimate the prevalence of true knot of the umbilical cord (TKUC) and identify associated adverse maternal and neonatal outcomes.

Study Design A multicenter retrospective cohort study was conducted, including all women with singleton pregnancies who delivered between 24 and 42 weeks of gestation from 2005 to 2021 at two large obstetrical centers. Gross pathological examinations of the placenta and umbilical cord were routinely performed immediately after delivery. Women with TKUC detected postpartum were compared with those without TKUC. Maternal and neonatal characteristics, along with adverse outcomes, were compared between the two groups.

Results During the study period, 283,055 deliveries met inclusion and exclusion criteria. The incidence of TKUC was 1.3%, intrauterine fetal death (IUFD) rate was significantly higher in the TKUC group (1.8% vs. 0.3%), with 91% of these deaths occurring after 34 weeks of gestation, and 72% occurring after 37 weeks. Women with TKUC experienced higher rates of preterm premature rupture of membranes, premature rupture of membranes, induction of labor, meconium-stained amniotic fluid, vacuum-assisted vaginal delivery, and postpartum hemorrhage. The rate of intrapartum cesarean deliveries was similar between the groups. Neonatal outcomes revealed similar birth weights, but higher rates of small-for-gestational-age neonates, low Apgar scores, jaundice, hypoglycemia, and intracranial hemorrhage in the TKUC group. Multivariate analysis demonstrated that TKUC was independently associated with IUFD (adjusted odds ratios [aOR]: 6.07; 95% confidence intervals [CI]: 4.68–7.86, $p < 0.01$).

Conclusion TKUC is not uncommon and is associated with an increased risk of IUFD, particularly in the late third trimester, as well as adverse neonatal outcomes. Early diagnosis in the third trimester followed by delivery in the late preterm or early term period may reduce IUFD rates.

Keywords

- ▶ true knot of the umbilical cord
- ▶ intrauterine fetal death
- ▶ adverse neonatal outcomes
- ▶ prevalence
- ▶ multicenter retrospective cohort
- ▶ pathological examination

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Key Points

- TKUC occurred in 1.3% of approximately 300,000 deliveries.
- It is associated with a sixfold higher risk of IUFD.
- Most IUFDs (91%) occurred > 34 weeks, with 72% occurring > 37.
- Third-trimester ultrasound and delivery at approximately 37 weeks may reduce IUFD.

True knots of the umbilical cord (TKUC) are estimated to occur in 1 to 1.25% of singleton pregnancies.^{1–6} The precise timing of TKUC formation remains debated. Some suggest that it occurs early in pregnancy, during the late first trimester, when the amniotic fluid volume is high relative to fetal size, while others believe it primarily forms during labor.⁷ An excessively long umbilical cord might act as a preventive factor against intrauterine fetal death (IUFD).⁸ Risk factors for TKUC include advanced maternal age, increased parity, polyhydramnios, diabetes mellitus, and male fetuses.^{3,9} However, recent studies indicate that children born with TKUC do not face an increased risk of long-term neurological complications.¹⁰

TKUC has been associated with various adverse perinatal outcomes, including IUFD, nonreassuring fetal heart rate, cesarean deliveries (CD) due to nonreassuring fetal heart rate, meconium-stained amniotic fluid, and lower Apgar scores^{2–4,9,11–13} Although rare, IUFD is more common in pregnancies affected by TKUC beyond 37 weeks of gestation, with the rate being 4 to 10 times higher compared to the general fetal population, reaching an incidence of 1% at term.^{2,4}

Despite the association between TKUC and adverse outcomes, the majority of ultrasound and obstetric societies do not currently advocate for routine screening for umbilical cord abnormalities, as most cases are only identified after delivery.¹⁴ However, recent advancements in ultrasound technology have significantly improved detection rates, suggesting that TKUC could potentially be identified during pregnancy.^{15–19} The decision to perform targeted ultrasounds for TKUC requires careful consideration of their clinical utility. While diagnosing TKUC during pregnancy might offer some benefits, it is essential to balance these against the added stress, unnecessary follow-ups, and potential risks of preterm deliveries and elective CD. Robust evidence of clear clinical benefits is needed before implementing such screenings.

The aims of this study were to investigate the prevalence of TKUC and to explore its clinical significance, including its association with IUFD and other adverse pregnancy outcomes in a large contemporary cohort.

Materials and Methods

Study Design

This multicenter retrospective cohort study was conducted at two large university-affiliated obstetrical centers. All antepartum and delivery care were covered by the National Health Plan. Data were retrieved from electronic medical records, which are recorded in real-time at the point of care by attending caregivers during labor and delivery. Summary notes in the medical records include an updated list of

pertinent diagnoses, following the International Classification of Diseases, which is revised by the attending physician before discharge. The medical records primarily consist of fixed, obligatory fields (such as abnormal findings in the umbilical cord or placenta) that must be completed before the patient is transferred to the postpartum ward. An additional search for the term “true knot of cord” was conducted in the summary notes of labor and CDs. Gross pathological examinations of the placenta and umbilical cord were routinely performed immediately after delivery. This study was approved by the institutional review boards of SZMC and BHMC (IRB approval number: 0125-24-SZMC).

Study Population

The study population included all women with a singleton pregnancy who delivered between 24 and 42 weeks of gestation from 2005 to 2021. Women with multifetal gestations, deliveries before 24 weeks (the national viability limit), out-of-hospital deliveries, and charts with missing data were excluded.

Study Outcomes

Maternal and neonatal characteristics and adverse outcomes were compared between women with a postpartum diagnosis of TKUC (study group) and those without TKUC (control group). The primary outcome of this study was the rate of IUFD. Secondary outcomes included adverse maternal and neonatal events. Maternal outcomes encompassed placental abruption, mode of delivery, admission to the maternal intensive care unit, postpartum hemorrhage, blood product transfusion, and placental disorders during the third stage of labor. Neonatal outcomes included perinatal death, neonatal birth weight, low Apgar scores (<7), neonatal asphyxia, and neonatal intensive care unit (NICU) admission, among others.

Statistical Analysis

Descriptive statistics were used to summarize characteristics, with proportions for nominal variables, means \pm standard deviations (SD) for normally distributed continuous variables, and medians with interquartile ranges (IQR) for nonnormally distributed continuous variables. Categorical variables were compared using the chi-square test or Fisher’s exact test, while continuous variables were analyzed using the unpaired Student’s *t*-test or Mann–Whitney test, as appropriate.

Univariate analysis was conducted to test associations between the presence of TKUC and various maternal demographic, obstetric, and delivery characteristics. A *p*-value <0.05 was considered statistically significant. We further employed multivariate analysis to evaluate the association between TKUC and IUFD. Variables found to be significant in

the univariate analysis were included in a multivariate logistic regression model to assess the association between TKUC and IUFD. These variables included maternal age, gravidity, parity, miscarriages (including more than three miscarriages), hypertensive disorders of pregnancy, diabetes of pregnancy, and nonvertex presentation. The results of these analyses are reported as adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CIs).

All statistical tests were two-sided, and analyses were conducted using SPSS software (version 25; IBM, Armonk, NY).

Results

During the study period, 283,055 deliveries met inclusion and exclusion criteria. Among them, 3,613 were postnatally diagnosed with TKUC, resulting in an incidence rate of 1.3% (→Fig. 1).

→Table 1 displays maternal demographic and obstetric characteristics, comparing the study and control groups.

Women in the TKUC were older, with higher gravidity and parity, higher rates of having at least one previous miscarriage, having at least 3 or more miscarriages, hypertensive and diabetes disorders of pregnancy.

The pregnancy and delivery outcomes are presented in →Table 2.

Primary Outcome

IUFD rates were significantly higher in the study group (1.8%) as compared to the control group (0.3%), $p < 0.01$. Mean gestational age at delivery and the rates of preterm labor were similar between the groups.

The following outcomes were more common in the study group: preterm premature rupture of membranes, premature

rupture of membranes, induction of labor, meconium-stained amniotic fluid, vacuum delivery, and postpartum hemorrhage. The intrapartum CD rate was similar between the groups.

→Fig. 2 demonstrates the rates of IUFD by gestational age groups for those with and without TKUC. Most cases of IUFDs (67%) in the TKUC group occurred between 37 and 40 weeks as opposed to 33% of the IUFD cases in the nonTKUC group, $p < 0.01$.

→Fig. 3 presented a Kaplan–Meier survival curve of those who had IUFD with and without TKUC. Almost all IUFD cases (91%) in the TKUC group occurred after 34 weeks of gestation versus 46% in the nonTKUC group, while 72%, occurred after 37 weeks of gestation versus 35% in the nonTKUC group.

Neonatal outcomes are shown in →Table 3. Rates of the following outcomes were higher among those with TKUC—small for gestational age neonate (SGA, less the 10th percentile), 1-minute Apgar score < 7 , 5-minute Apgar score < 7 , jaundice, hypoglycemia, and intracranial hemorrhage.

An adjusted multivariable logistic regression analysis for significant covariates and confounders was applied to examine the association between TKUC and IUFD. This analysis revealed that TKUC is independently associated with IUFD (aOR: 6.07; 95% CI: 4.68–7.86, $p < 0.01$), →Table 4.

Discussion

Principal Findings

This multicenter retrospective cohort study aimed to evaluate the prevalence of TKUC and assess associated adverse pregnancy outcomes. The incidence of TKUC in this cohort was 1.3%, and TKUC was independently associated with a sixfold increase in the risk of IUFD. The risk of IUFD was notably higher

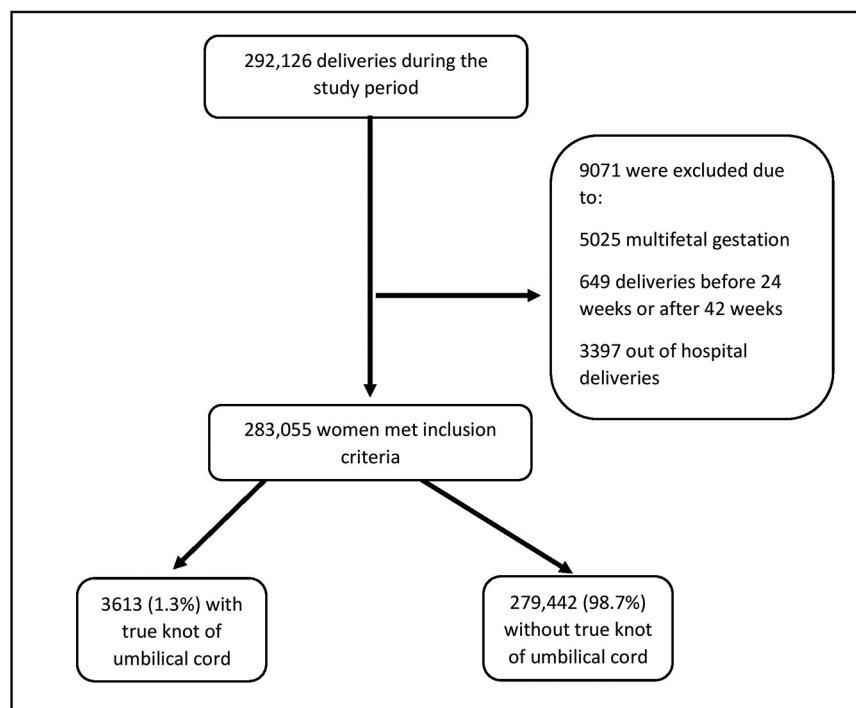


Fig. 1 Study flow chart.

	No TKUC <i>n</i> = 279,404	TKUC <i>n</i> = 3,613	<i>p</i> -Value
Maternal age, y	28.9 ± 5.8	30.7 ± 5.8	<0.01
Gravidity	4.1 ± 3	5 ± 3.1	<0.01
Parity	3.6 ± 2.5	4.4 ± 2.6	<0.01
Miscarriage, any	82,581 (29.6%)	1,322 (36.6%)	<0.01
Previous miscarriages ≥ 3	10,907 (3.9%)	216 (6%)	<0.01
Previous cesarean delivery, any	33,124 (11.9%)	407 (11.3%)	0.28
Pregnancy conceived by fertility treatments	7,662 (2.7%)	92 (2.5%)	0.47
Hypertensive disorders of pregnancy	6,213 (2.2%)	102 (2.8%)	0.02
Diabetes (pregestational and gestational)	11,242 (4%)	206 (5.7%)	<0.01
Polyhydramnios	3,302 (1.2%)	35 (1%)	0.24

Abbreviation: TKUC, true knot of the umbilical cord.

Note: Data are mean ± standard deviation; number (%).

	No TKUC <i>n</i> = 279,404	TKUC <i>n</i> = 3,613	<i>p</i> -Value
Primary outcome			
Intrauterine fetal death	898 (0.3%)	64 (1.8%)	<0.01
Secondary outcomes			
Gestational age at delivery	39.3 ± 1.7	39.2 ± 1.7	0.47
Preterm delivery at less than 37 wks	11,854 (4.2%)	168 (4.6%)	0.23
Nonvertex presentation	7,767 (2.8%)	42 (1.2%)	<0.01
Preterm premature rupture of membranes	1,723 (0.6%)	33 (0.9%)	0.02
Premature rupture of membranes	31,755 (11.4%)	487 (13.5%)	<0.01
Induction of labor	27,665 (10.2%)	475 (13.3%)	<0.01
Meconium-stained amniotic fluid	43,883 (15.7%)	759 (21%)	<0.01
Chorioamnionitis	3,238 (1.2%)	35 (1%)	0.29
Intrapartum cesarean delivery	12,527 (4.5%)	142 (3.9%)	0.11
Vacuum assisted vaginal delivery	14,861 (5.3%)	149 (4.1%)	<0.01
Postpartum hemorrhage	21,276 (7.6%)	204 (5.6%)	<0.01
Blood products transfusion	2,881 (1%)	27 (0.7%)	0.09
Puerperal fever	4,264 (1.5%)	53 (1.5%)	0.77

Abbreviation: TKUC, true knot of the umbilical cord.

Note: Data are mean ± standard deviation; number (%).

beyond 34 weeks of gestation. Additionally, TKUC was associated with increased rates of complications, including preterm premature rupture of membranes, premature rupture of membranes, induction of labor, meconium-stained amniotic fluid, vacuum-assisted delivery, postpartum hemorrhage, SGA neonates, low Apgar scores, jaundice, hypoglycemia, and intracranial hemorrhage. However, the rates of intrapartum CDs were similar between the groups.

Results in the Context of What Is Known

Previous studies have reported the occurrence of TKUC in 0.8 to 1.25% of singleton pregnancies, consistent with the findings of this study^{2-5,9} Retrospective studies examining the association between TKUC and IUFD have yielded inconsistent results. Weissman-Brenner et al⁴ reported a

tenfold increase in IUFD beyond 37 weeks of gestation. Similarly, Linde et al²⁰ found a fourfold increase in IUFD, while Sørnes et al²¹ observed a tenfold increase in the likelihood of IUFD. Conversely, Houry et al⁹ noted a higher rate of IUFD in the TKUC group, but this did not reach statistical significance. Furthermore, Suzuki et al⁸ reported a decreased risk of IUFD in singleton pregnancies delivered after 34 weeks.

In our study, most IUFD cases occurred after 34 weeks of gestation, with a notably higher risk between 37 and 40 weeks. This significant finding suggests that antepartum diagnosis and early intervention—such as delivery at the late preterm period after 34 weeks of gestation or early term at 37 weeks to avoid preterm complications—may be crucial in reducing the risk of IUFD in these pregnancies.

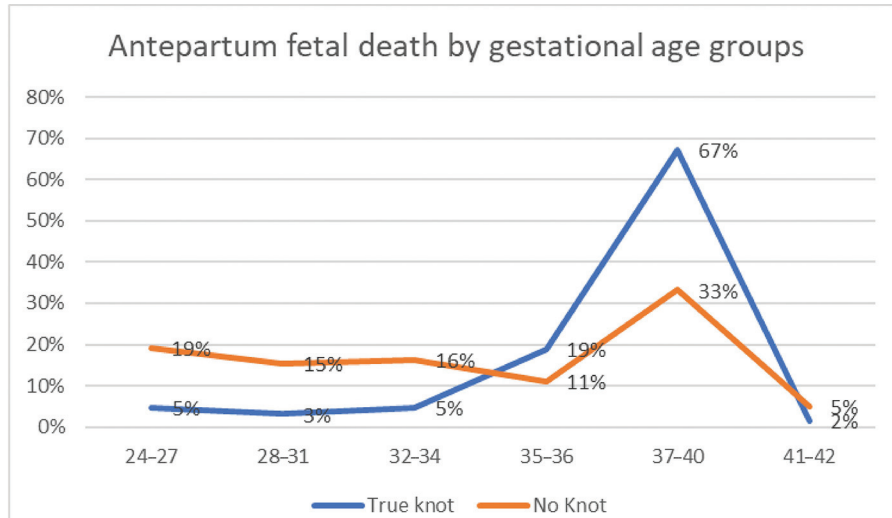


Fig. 2 IUF rates by gestational age groups for those with and without TKUC. IUF, intrauterine fetal death; TKUC, true knot of the umbilical cord.

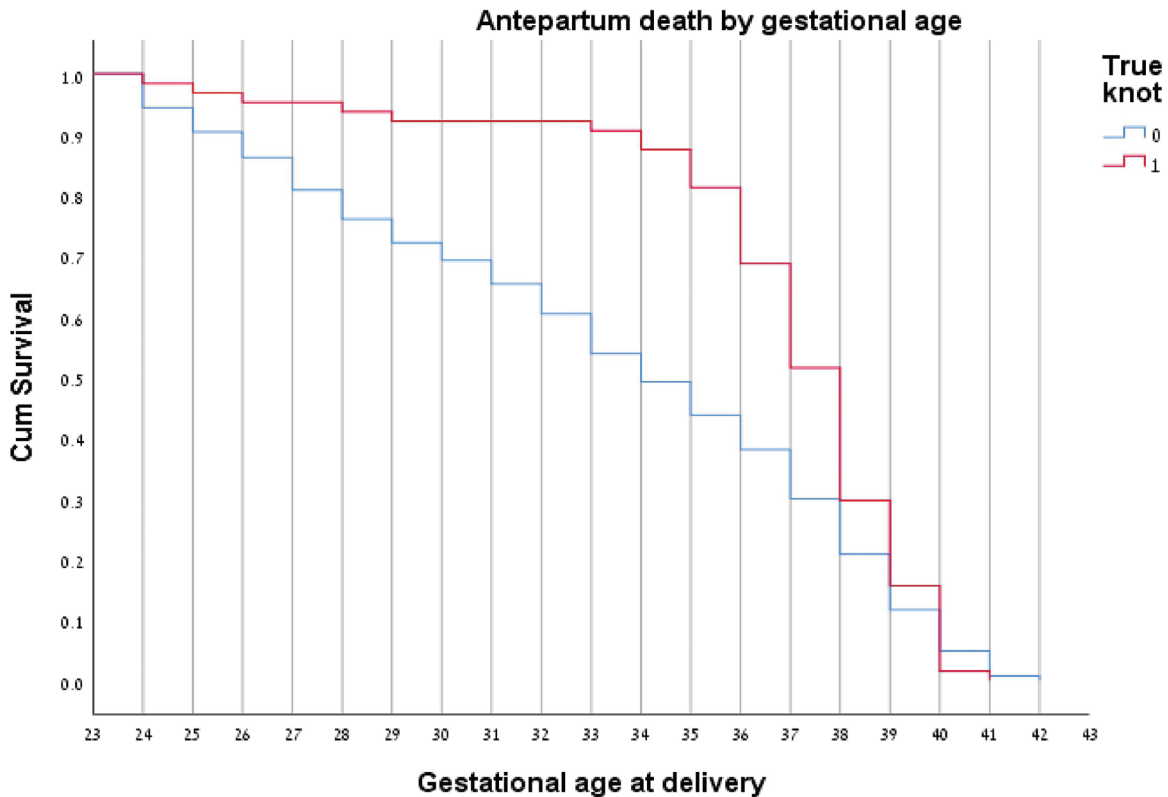


Fig. 3 Kaplan-Meier survival curve of those who had IUF with and without TKUC. IUF, intrauterine fetal death; TKUC, true knot of the umbilical cord.

We did not find an increased rate of intrapartum CD associated with TKUC. However, we observed an association with adverse neonatal outcomes. Similar to the findings of Lichtman et al,¹⁰ our study showed higher rates of low Apgar scores (<7) and SGA infants. Airas et al² also reported that low Apgar scores at 1 minute were significantly more frequent in the TKUC group compared to the general obstetric population, despite a lower frequency of CD. Likewise, Hershkovitz et al³ found an increased incidence of fetal distress and meconium-stained amniotic fluid, along with

a higher risk of CD. Houry et al⁹ reported higher rates of 1-minute Apgar scores below 7 and neonatal seizures in the TKUC group.

In contrast, Bohiltea et al¹³ found that the primary adverse neonatal outcome was due to iatrogenic prematurity, driven by maternal anxiety following the prenatal diagnosis and mode of delivery. Carter et al²² found no significant difference in neonatal morbidity, while Weissbach et al²³ indicated that active management, compared to routine management, did not reduce neonatal asphyxia-related

Table 3 Neonatal outcomes stratified by postpartum diagnosis of TKUC

	No TKUC n = 279,404	TKUC n = 3,613	p-Value
Birthweight, g	3,300 ± 487	3,312.2 ± 504.7	0.13
LGA	30,233 (10.8%)	406 (11.3%)	0.42
SGA	18,254 (6.5%)	267 (7.4%)	0.04
1-min Apgar score < 7	8,690 (3.1%)	186 (5.1%)	<0.01
5-min Apgar score < 7	3,232 (1.2%)	100 (2.8%)	<0.01
Birth asphyxia	1,672 (0.6%)	17 (0.5%)	0.32
NICU admission	12,689 (4.5%)	183 (5.1%)	0.11
Meconium aspiration syndrome	400 (0.1%)	8 (0.2%)	0.22
Jaundice	15,187 (5.4%)	232 (6.4%)	0.01
Transient tachypnea of the newborn	4,661 (1.7%)	56 (1.6%)	0.59
Mechanical ventilation	3,492 (1.3%)	35 (1%)	0.13
Seizures	2,636 (0.9%)	34 (0.9%)	0.99
Hypoglycemia	11,691 (4.2%)	194 (5.4%)	<0.01
Sepsis	818 (0.3%)	15 (0.4%)	0.18
Encephalopathy	143 (0.1%)	2 (0.1%)	0.91
Intracranial hemorrhage	772 (0.3%)	2 (0.1%)	0.01

Abbreviations: LGA, large for gestational age, NICU, neonatal intensive-care unit; SGA, small for gestational age, TKUC, true knot of the umbilical cord.

Note: Data are mean ± standard deviation; number (%).

Table 4 Multivariate logistic regression analysis for the association between TKUC and intrauterine fetal death

	p-Value	aOR	95% CI	
Nonvertex presentation	<0.01	9.94	8.48	11.67
True knot	<0.01	6.07	4.68	7.86
Hypertensive disorders of pregnancy	<0.01	1.63	1.18	2.24
Parity	0.19	1.12	0.95	1.32
Miscarriages, any	0.32	1.14	0.88	1.46
Maternal age, y	0.37	0.99	0.98	1.01
Gravidity	0.65	0.96	0.82	1.14
Diabetes (pregestational and gestational)	0.82	1.03	0.77	1.38
Miscarriages ≥ 3	0.82	1.06	0.64	1.75

Abbreviations: aOR: adjusted odds ratio; CI: confidence interval; TKUC, true knot of the umbilical cord.

adverse outcomes. Instead, it increased CD rates, induced prematurity, and NICU admissions.

Our findings of increased IUFD occurrence after 34 weeks, particularly between 37 and 40 weeks, suggest that antenatal diagnosis of TKUC and early intervention, such as delivery, may be crucial in reducing the risk of IUFD in these pregnancies. Most ultrasound and obstetrical societies do not recommend routine screening for TKUC. Deciding to perform targeted ultrasounds to detect true knots requires weighing clinical utility, feasibility, and potential risks. While such examinations could enhance prenatal care by identifying significant anomalies, they also pose challenges, including increased psychological stress on patients and risks of preterm birth and CD. Given the low risk of IUFD before 34 weeks and the uncertainty of when TKUCs occur, screening during the early third trimester, around 32 weeks, might be appropriate.

Clinical Implications

Our study suggests that TKUC is not a rare finding, and when detected in the third trimester, either incidentally or through targeted screening, the increased risk of IUFD and other adverse outcomes should be a significant concern in managing such pregnancies. It is plausible that closer monitoring and potentially earlier delivery may be warranted to mitigate these risks. However, the decision to implement targeted ultrasound screenings for TKUC must be carefully balanced against potential drawbacks, such as increased maternal anxiety, cost-effective analysis of screening the umbilical cord for TKUC in the third trimester, and the risks associated with unnecessary interventions. Further research is necessary to establish clear clinical guidelines and determine the optimal management strategies for pregnancies affected by TKUC.

Research Implications

Several unanswered questions remain regarding the pathophysiology and optimal management of TKUC. Future research should focus on the sensitivity and specificity of prenatal detection, particularly in the early third trimester, to reduce the anxiety that may accompany a prolonged period of monitoring. Additionally, studies exploring the efficacy of different monitoring and intervention strategies for pregnancies affected by TKUC are needed. Further longitudinal studies tracking the long-term neurodevelopmental outcomes of infants born with TKUC would also be valuable in fully understanding the implications of this condition.

Strengths and Limitations

The strengths of this study include its large sample size and the use of comprehensive, real-time electronic medical records, which enhance the reliability and generalizability of the findings. The multicenter design adds to the robustness of the results. However, the retrospective nature of the study introduces potential selection bias and limits the ability to establish causality. Additionally, the reliance on gross pathological examinations for TKUC diagnosis may lead to underreporting or misclassification. Due to limited data, we did not compare placental pathology for IUFD with and without TKUC and do not have information about detailed anatomy scans done during the pregnancy. Moreover, most of the outcomes are postpartum from live infants, and postmortem autopsy was not performed for IUFD. Despite these limitations, the study provides significant insights into the association between TKUC and adverse perinatal outcomes, contributing valuable evidence to the existing body of literature.

Conclusion

This multicenter retrospective cohort study has highlighted the significant association between TKUC and increased rates of IUFD and other adverse neonatal outcomes. With an incidence of 1.3%, TKUC presents a substantial risk, particularly beyond 34 weeks of gestation, underscoring the need for prenatal detection and timely intervention in pregnancies affected by TKUC. The study's findings advocate for further research to establish optimal monitoring and management strategies for pregnancies complicated by TKUC, aiming to improve perinatal outcomes while minimizing unnecessary interventions.

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None.

Conflict of Interest

None declared.

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