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MATERNAL-FETAL MEDICINE

The perils of true knot of the umbilical cord: antepartum, intrapartum and postpartum complications and clinical implications

Alina Weissmann-Brenner[1,2] · Raanan Meyer[1,2] · Noam Domniz[1,2] · Gabriel Levin[3] · Natav Hendin[2] · Rakefet Yoeli-Ullman[1,2] · Shali Mazaki-Tovi[1,2] · Tal Weissbach[1,2] · Eran Kassif[1,2]

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Abstract

Background True knot of the umbilical cord (TKUC) is found in 0.3–2.1% of pregnancies and is associated with an increased risk of adverse perinatal outcomes.

Methods A retrospective cohort study including all singleton pregnancies delivered from 2011 to 2019 was performed. Diagnosis of TKUC was made postnatally, immediately after delivery of the baby. Comparison was made between pregnancies with and without TKUC regarding maternal, fetal and neonatal adverse outcome.

Results Overall, 867/85,541 (1%) pregnancies were diagnosed with TKUC. Maternal age, BMI, gravidity and parity were significantly higher in pregnancies with TKUC as well as higher rate of induction of labor, meconium-stained amniotic fluid, and delivery prior to 37 weeks. The rate of cesarean deliveries due to non-reassuring-fetal monitor was significantly higher in pregnancies with TKUC. Overall, there were 2.5% IUFD in pregnancies with TKUC vs. 1% in pregnancies without TKUC ($p < 0.001$). Importantly, the rate of IUFD prior to 37 weeks of gestation was not significantly higher in the group with TKUC, however, the rate of IUFD after 37 weeks of gestation was 10 folds higher in fetuses with TKUC, 0.9% vs. 0.08% ($p < 0.001$). Significantly, more neonates with TKUC needed phototherapy or suffered from hypoglycemia. There were no differences in the 5 min Apgar scores, admission to the NICU and number of days of hospitalization.

Conclusion Pregnancies complicated with TKUC are associated with a tenfold higher risk of IUFD beyond 37 weeks of gestation. To the results of this study suggest that it would be prudent to induce labor around 37 weeks of gestation in pregnancies with prenatal diagnosis of TKUC. It may be warranted to use continuous fetal monitoring during labor and delivery in those cases were antenatal diagnosis of TKUC is made.

Keywords True knot · Umbilical cord · Cesarean section · Intrauterine fetal death

Introduction

True knot of the umbilical cord (TKUC) is present in 0.3–2.1% of singleton pregnancies [1–4]. Several studies have reported that the rate of fetal growth restriction (FGR) is higher in pregnancies with TKUC compared to controlled, presumably due to constriction of the umbilical cord and consequently reduction in fetal blood flow [5, 6]. Others reported increased rate of four-fold to eight-fold higher rates of fetal death (FD) in the second and third trimesters [7, 8] and also intrapartum fetal death even in the setting of normal intermittent fetal heart rate auscultation [9, 10]. While the exact mechanism for the association between TKUC and fetal death is not completely clear, it has been theorized that FD is secondary to a sudden severe tightening of the umbilical cord, resulting in its occlusion and total deprivation of blood and oxygen supply to the fetus [4]. While presence of TKUC is associated with higher IUFD rates, a recent study concluded that its presence does not appear to impact the long-term neurological health of exposed the offspring, similar to other conditions of umbilical cord [11, 12].

✉ Alina Weissmann-Brenner
alinabrenner@yahoo.com

[1] The Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center, Tel Hashomer, 52621 Ramat Gan, Israel

[2] The Sackler School of Medicine Tel Aviv University, Tel Aviv, Israel

[3] The Department Gynecologic Oncology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

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Despite the aforementioned findings, there is a paucity of up-to-date studies addressing the prevalence and the association between this finding and maternal, fetal and neonatal adverse outcomes.

Thus, the objective of this study was to determine risk factors associated with TKUC, as well as adverse maternal, fetal and neonatal outcomes associated with TKUC.

Materials and methods

A retrospective cohort study was performed at a single tertiary center between the years 2011–2019.

Inclusion criteria included: (1) singleton gestations, (2) diagnosis of true TKUC immediately following delivery. Exclusion criteria included twins and high-order multiple pregnancies. The study cohort was divided into two groups: (1) study group (pregnancies with TKUC) and (2) controls (pregnancies without TKUC).

Diagnosis of TKUC was made after delivery by midwife or obstetrician. The following data were extracted: maternal characteristics including age, body mass index (BMI), substance abuse (including smoking, alcohol), pre-gestational diabetes mellitus, mode of conception, gravidity and parity. Data regarding pregnancy outcomes included: gestational diabetes mellitus, hypertensive disorders of pregnancy, gestational age at delivery, mode of delivery, presence of meconium-stained amniotic fluid and FD. Neonatal characteristics included: birthweight, neonatal gender, 5-min Apgar score, admission to neonatal intensive care unit (NICU), convulsions, blood transfusions, phototherapy due to hyperbilirubinemia, hypoglycemia and need for mechanical ventilation.

The study was approved by the local Institutional Review Board.

Statistical analysis

Characteristics of women and neonates are described as proportions for categorical variables and as means and standard deviation for continuous variables. Significance was assessed by χ^2 test and—Fisher's exact test for categorical variables. Student *t* test was used for analysis of continuous variables with normal distribution and Mann–Whitney *U* test for analysis of continuous variables with skewed distribution. Study results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). A two-sided p value < 0.05 indicated statistical significance. A multivariable regression analysis was performed to identify independent factors associated with the occurrence of TKUC or adverse neonatal outcome among TKUC pregnancies. The data were analyzed using Software Package for Statistics and Simulation (IBM SPSS version 22, IBM Corp, Armonk, NY).

Results

The study cohort included 85,541 deliveries who met the inclusion and exclusion criteria. Of those, 867 (1%) were diagnosed with TKUC. Clinical and demographic characteristic are presented in Table 1. Maternal age, BMI, gravidity and parity were significantly higher in the study group with TKUC. Significantly more patients with TKUC had hypertensive disorders of pregnancy, underwent external cephalic version, underwent induction of labor, and delivered prior to 37 weeks of gestation. The rate of meconium-stained amniotic fluid was on the verge of a significant difference and was higher in the study group.

The overall rate of cesarean deliveries (CD) did not differ between the groups ($p = 0.57$). However, the rate of CD due to non-reassuring fetal monitor was significantly higher in pregnancies with TKUC (56.9% with TKUC vs. 35.4% without TKUC, $p < 0.001$).

Fetal death (FD) was significantly more common in the TKUC group. Overall, there were 22 pregnancies with FD (2.5%) in the study group vs. 865 (1%) in the control group ($p < 0.001$). Importantly, the rate of FD was substantially higher after 37 weeks of gestation reaching 0.9% in pregnancies with TKUC vs. 0.08% in pregnancies without TKUC ($p < 0.001$). There was no significant statistical difference in the rate of FD prior to 37 weeks of gestation.

Postnatally, more neonates with TKUC needed phototherapy or suffered hypoglycemia. There were no in between-groups differences in the rate of 5 min Apgar scores, admission to the NICU and number of hospitalization days. In the study group with TKUC, there were no cases of neonatal death during the first 24 h following delivery. The mean birthweight was significantly lower and there were significantly more males in the TKUC group compared to controls.

Multivariable analysis of the risk factors associated with TKUC is presented in Table 2. Advanced maternal age and male gender were significantly and independently associated with TKUC.

Multivariable analysis of risk of adverse outcomes associated with TKUC is presented in Table 3. The rate of overall FD, FD ≥ 37 weeks of gestation, preterm delivery and meconium-stained amniotic fluid was significantly higher in pregnancies with TKUC. Significantly more neonates with TKUC suffered from hypoglycemia and needed phototherapy.

Within the study group, there were significantly more CD due to non-reassuring fetal heart rate after 37 weeks

Table 1 Characteristics of study population

	Pregnancies with true knot $n=867$ n (%)	Control group $n=85,541$	OR	p value
Maternal age ± SD	33.3 ± 5.1	32.1 ± 5.1	1.52 (1.32–1.74)	< 0.001
Maternal age ≥ 35	362 (41.8%)	27,396 (32.0%)	1.50 (1.31–1.71)	< 0.001
BMI ± SD	28.6 ± 4.6	28.1 ± 4.4	1.23 (1.06–1.42)	0.001
Obese (BMI > 30)	265 (30.6%)	22,506 (26.3%)	1.22 (1.06–1.40)	0.005
Smoking	38 (4.5)	3979 (4.8)		0.68
Alcohol	3 (0.4)	166 (0.2)		0.32
Characteristics of pregnancy				
Fertility Tx	127 (14.6)	13,631 (15.9%)		0.30
Gravidity	3.17 (1.99)	2.74 (1.87)	0.61 (0.51–0.72)	< 0.001
Primigravid	170 (19.6%)	24,442 (28.6%)	0.61 (0.52–0.72)	< 0.001
Parity	1.57 (1.43)	1.23 (1.41)	0.53 (0.45–0.62)	< 0.001
Nulliparous	203 (23.4%)	31,103 (36.4%)	0.52 (0.45–0.61)	< 0.001
Previous CD	131 (15.1)	13,589 (15.9)		0.53
Previous > 1 CD	33 (3.8)	3905 (4.6)		0.28
Gestational DM	90 (10.4)	7712 (9.0)		0.16
Pregestational DM	12 (1.4)	741 (0.9)		0.10
HTN/PET	50 (5.8)	3449 (4.0)	1.45 (1.09–1.94)	0.01
Characteristics of delivery				
GA at delivery ± SD	38.9 (2)	39.1 (2)	0.95 (0.93–0.98)	0.002
GA < 37 weeks	81 (9.3)	6144 (7.2)	1.33 (1.05–1.67)	0.01
GA < 32 weeks	14 (1.6)	1108 (1.3)		0.40
Spontaneously onset of labor	416 (48.0)	45,034 (52.6)	0.83 (0.72–0.94)	0.006
Elective CD	118 (13.6)	14,557 (17.0)	0.76 (0.63–0.93)	0.008
Induction/augmentation of labor	263 (30.3)	20,993 (24.5)	1.33 (1.15–1.54)	< 0.001
ECV	4 (0.5)	143 (0.2)	2.76 (1.02–7.49)	0.03
Mode of delivery				
NVD	612 (70.6)	59,473 (69.6)		0.52
Operative vaginal delivery	51 (5.9)	5245 (6.1)		0.76
Cesarean n (%)	204 (23.5)	20,823 (24.3)		0.57
Elective CD	81 (9.3)	11,107 (13.0)	0.69 (0.54–0.86)	0.001
Indication of cesarean				
NRFHR	70/123 (56.9%)	3440/9716 (35.4%)	2.40 (1.68–3.45)	< 0.001
Meconium	145 (16.7)	12,327 (14.4)	1.19 (0.99–1.42)	0.05
Cord prolapse	2 (0.2)	71 (0.1)		0.13
Cord presentation	0 (0)	19 (0.0002)		1.0
Characteristics of neonates				
Birthweight ± SD	3159 ± 559	3200 ± 533	0.93 (0.87–0.99)	0.02
Male	518 (59.7)	43,761 (51.2)	1.41 (1.23–1.62)	< 0.001
Apgar 5 < 7	1 (0.1)	296 (0.3)		0.38
PH vein ± SD	7.27 ± 0.06	7.26 ± 0.07		0.03
PH vein ≤ 7	0 (0)	123 (0.1)		0.639
PH artery ± SD	7.24 ± 0.07	8.24 ± 0.07		0.99
PH artery ≤ 7	1 (0.1%)	167 (0.2%)		1.00
Death within 24 h	0 (0)	44 (0.1)		1.0
Death within 1 month	0 (0)	77 (0.1)		1.0
NICU admission	39 (4.5)	3108 (3.6)		0.17
NICU in deliveries ≥ 37	14/786 (1.8%)	1164/79,394 (1.5%)		0.46
NICU in deliveries < 37 n(%)	25/81 (30.9%)	1943/6,144 (31.6%)		0.88
Days hospitalization neonate	4.95 (8.15)	4.57 (5.96)		0.17

Table 1 (continued)

	Pregnancies with true knot $n=867$ n (%)	Control group $n=85{,}541$	OR	p value
Convulsions/seizures	2 (0.2)	96 (0.1)		0.25
Asphyxia	3 (0.3)	70 (0.1)	4.24 (1.33–13.4)	0.03
Oxygen enrichment	21 (2.4)	1462 (1.7)		0.10
Blood transfusion	7 (0.8)	408 (0.5)		0.16
Phototherapy	86 (9.9)	5685 (6.6)	1.54 (1.23–1.93)	< 0.001
High flow nasal cannula	12 (1.4)	861 (1.0)		0.30
Transitory tachypnea	7 (0.8)	1001 (1.2)		0.32
Hypoglycemia	68 (7.8)	4563 (5.3)	1.51 (1.17–1.93)	0.001
IUFD	22 (2.5)	865 (1.0)	2.54 (1.66–3.91)	< 0.001
≥ 37	8 (0.9)	67 (0.08)	12.1 (5.8–25.4)	< 0.001
34–37	3 (0.3)	99 (0.1)		0.10
< 34	11 (1.2)	699 (0.8)		0.13
Mechanical ventilation	12 (1.4)	769 (0.9)		0.14
HIE	3 (0.3)	80 (0.1)	3.70 (1.16–11.76)	0.05
RDS	10 (1.2)	682 (0.8)		0.24

SD standard deviation, *BMI* body mass index, *Tx* treatment, *CD* cesarean delivery, *DM* diabetes mellitus, *HTN* hypertension, *PET* preeclampsia, *GA* gestational age, *NVD* normal vaginal delivery, *ECV* external cephalic version, *NRFHR* non-reassuring fetal heart rate, *NICU* neonatal intensive care unit, *HIE* Hypoxic ischemic encephalopathy, *RDS* respiratory distress syndrome

Table 2 Multivariate regression analysis of risk factors associated with true knot in the umbilical cord

	aOR (95% CI)	p value
Maternal age	1.03 (1.01–1.04)	< 0.001
BMI	1.01 (1.00–1.03)	0.052
Gravidity	1.00 (0.94–1.08)	0.82
Parity	1.09 (1.00–1.19)	0.38
PET	1.34 (0.99–1.81)	0.053
Pregestational DM	1.20 (0.65–2.21)	0.54
Male	1.38 (1.20–1.59)	< 0.001

BMI body mass index, *PET* preeclampsia, *DM* diabetes mellitus

of gestation (7%) in comparison CD prior to 37 weeks of gestation (4%), $p < 0.001$.

Discussion

The results of this study suggest that TKUC is associated with a significantly higher risk of FD. Importantly, the additional risk associated with TKUC is limited to pregnancies after 37 weeks. In addition, TKUC is associated with increased rate of preterm deliveries, CD due to non-reassuring fetal heart monitor and meconium-stained amniotic fluid. Neonates with TKUC have increased risk of hypoglycemia and need for phototherapy, but without increased neonatal mortality.

In accordance with previous reports, the risk factors for TKUC in the present study included increased maternal age, higher BMI and parity [1, 2, 4]. These factors may be associated with a relatively large uterine volume that enables vigorous fetal movements and subsequently increased rate of a TKUC [1, 2, 4]. Hypertensive diseases of pregnancy and male fetuses were also reported to be associated with TKUC [1, 2, 4].

Although there was no difference in the overall rate of CD, there were significantly more CD due to non-reassuring fetal heart rate and more meconium-stained amniotic fluid during labor among pregnancies with TKUC. This was previously reported [1, 4] and may be related to pressure exerted (during contractions) on the umbilical cord leading to its partial constriction. Indeed, several case reports described intrapartum death of fetuses with TKUC [9, 10]. Therefore, it may be warranted to use continuous fetal monitoring during labor and delivery in those cases were antenatal diagnosis of TKUC is made.

The differences in the rates of IUFD between term and preterm pregnancies may be attributed to the increased uterine contractions at term, leading to compression on the TKUC and reduction of blood flow to the fetus. Experimental studies of cord compression in fetal sheep showed different responses of fetuses according to gestational age [13, 14]. In late pregnancy less of the fetal cardiac output is directed towards the placenta, but the fetal demand increases, which in turn increase the vulnerability for cord accident and obstruction of umbilical flow [13, 14].

Table 3 Analysis of risk of adverse outcomes associated with true knot in umbilical cord

	Cases 867	Controls 85,540	OR	*p* value	95% CI
IUFD	22 (2.5)	865 (1.0)	2.54	< 0.001	1.66–3.91
IUFD ≥ 37	8 (1.0)	67 (0.1)	11.88	< 0.001	5.68–24.80
IUFD 34–37	3 (0.3)	99 (0.1)	2.99	0.14	0.94–9.46
IUFD < 34	11 (1.2)	699 (0.8)	1.55	0.52	0.85–2.84
Delivery < 37	81 (9.3)	6144 (7.2)	1.33	0.01	1.06–1.67
Delivery 34–37	58 (6.7)	4447 (5.2)	1.30	0.04	1.00–1.70
Delivery < 34	23 (2.7)	1697 (2.0)	1.34	0.16	0.88–2.04
Delivery < 32	14 (1.6)	1108 (1.3)	1.25	0.40	0.73–2.12
CD	204 (23.5)	20,823 (24.3)	0.95	0.57	0.81–1.12
CD due to NRFHR	70 (8.0)	3440 (4.0)	2.09	< 0.001	1.63–2.68
OVD	51 (5.9)	5235 (6.1)	0.95	0.76	0.72–1.27
Meconium	145 (16.7)	12,327 (14.4)	1.19	0.05	0.99–1.42
5 min Apgar < 7	1 (0.1)	296 (0.3)	0.33	0.38	0.04–2.37
PH artery ≤ 7	1 (0.1)	167 (0.2)	0.59	0.59	0.08–4.22
NICU *n* (%)	39 (4.5)	3108 (3.6)	1.24	0.17	0.90–1.72
Convulsions/seizures *n* (%)	2 (0.2)	96 (0.1)	2.05	0.30	0.50–8.36
Asphyxia *n* (%)	3 (0.3)	70 (0.1)	4.24	0.03	1.33–13.49
Oxygen enrichment *n* (%)	21 (2.4)	1462 (1.7)	1.42	0.10	0.92–2.20
Blood transfusion *n* (%)	7 (0.8)	408 (0.5)	1.69	0.16	0.80–3.59
Phototherapy *n* (%)	86 (9.9)	5686 (6.6)	1.54	< 0.001	1.23–1.93
High flow nasal cannula *n* (%)	12 (1.4)	861 (1.0)	1.38	0.26	0.77–2.45
Transitory tachypnea *n*	7 (0.8)	1001 (1.2)	0.68	0.32	0.32–1.45
Hypoglycemia	68 (7.8)	4563 (5.3)	1.51	0.001	1.17–1.93
Mechanical ventilation	12 (1.4)	769 (0.9)	1.54	0.13	0.87–2.74
HIE	3 (0.3)	80 (0.1)	3.70	0.01	1.16–11.76
RDS	10 (1.2)	682 (0.8)	1.45	0.24	0.77–2.72
Composite	182 (21.0)	13,161 (15.4)	1.46	< 0.001	1.24–1.72

Composite: NICU admission, blood transfusion, hypoglycemia, transient tachypnea of the newborn, rds, oxygen treatment, nasal canula, mechanical ventilation, phototherapy, pH less than 7, apgar 5 less than 7, asphyxia, seizure, HIE, IUFD

NICU neonatal intensive care unit, *IUFD* intrauterine fetal death, *HIE* Hypoxic ischemic encephalopathy, *RDS* respiratory distress syndrome, *CD* cesarean delivery, *OVD* operative vaginal delivery

The absence of neonatal brain injury and post-natal mortality in the TKUC group supports the assumption that IUFD mechanism entails acute tightening of the umbilical cord, resulting in complete deprivation of oxygenated blood supply to the fetus [15]. This acute event with no prior warning signs, renders close fetal monitoring and surveillance inefficient in preventing IUFD. Similar to previous studies [1, 2], we found that there was probably no chronic fetal compromise during pregnancy, as can be concluded from the equivalent 5 min Apgar scores and the umbilical cord PH of the two groups. These data are in concordance to Maher et al. that found no differences in the umbilical cord gas values between pregnancies with TKUC and pregnancies without TKUC [1]. It should be mentioned that contrary to these data, Rainfassen et al. reported association between TKUC deliveries and admission to intensive care unit and low 5 min Apgar scores [3].

Our study has a number of strengths. It included large number of pregnancies diagnosed with TKUC. Furthermore, our study involved meticulous data extraction from admission, hospitalization and delivery charts—allowing for evaluation of a large number of variables of interest. Moreover, we did not rely on ICD coding (International Classification of Disease), rather on data recorded in real time at delivery charts, therefore minimizing information bias.

We acknowledge several limitations of our study. This study shares the limitations inherent to retrospective investigations and the findings are interpreted without randomization and strict control of all study aspects. In addition, we recognize that the cross-section natural of this study precludes comment on causality in the association between TKUC and adverse outcome. Finally, the tightening of the cord or the number of knots were not evaluated during pregnancy. Although prenatal diagnosis of TKUC is now feasible

[16], a prospective study on the accuracy of prenatal ultrasound in the detection of TKUC is still missing, and the outcome of these pregnancies are of utmost importance.

Prenatal identification of TKUC might lead to worries and frustrations both to the parents and the clinicians. Some argue that the prenatal knowledge is, therefore, unnecessary [17]. It was considered that there was little that can be done during pregnancy in order to prevent fetal death due to tightening of the knot [2]. It was also considered extremely inaccurate to diagnose TKUC in utero. Indeed, previous studies using 2DUS and Doppler ultrasound reported low detection rates of TKUC [18]. Earlier studies reported no detection rate using both second and third trimester 2DUS [18], while later studies on 3DUS reported 62% detection rate [19]. We have recently demonstrated that prenatal diagnosis of TKUC is feasible and accurate [16]. Out of 56 pregnancies suspected to have TKUC on ultrasound at midtrimester, 54 had indeed TKUC, yielding accuracy of 96.4%. We recommended to try to evaluate the umbilical cord during the Level II anatomical scan performed at midtrimester. Since the most consequential finding of the present study was the dramatic 10-fold increase of IUFD after 37 weeks of gestation in pregnancies complicated by TKUC, we recommend induction of delivery at 37 weeks in suspected cases with TKUC.

Conclusion

Due to the acute nature of IUFD, the absent of herald signs of IUFD and dramatic increased rate of IUFD after 37 weeks of gestation in pregnancies with TKUC, it seems prudent to advise induction of labor at early term in pregnancies diagnosed prenatally with TKUC, with continuous meticulous monitoring during all stages of labor. We believe that this management may lower the excess IUFD rate associated with pregnancies complicated with TKUC.

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Data availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest All the authors have made substantial contributions to the concept, data interpretation, drafting or critical revision of the manuscript for intellectual content and have approved the final version. There are no conflicts of interest for the authors.

Ethical approval The study was approved by the IRB board of the Chaim Sheba Medical center No. 2987-16-SMC.

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