Prenatal diagnosis of a lean umbilical cord: a simple marker for the fetus at risk of being small for gestational age at birth

L. Raio, F. Ghezzi*, E. Di Naro†, M. Franchi*, E. Maymon‡, M. D. Mueller and H. Brühwiler

Department of Obstetrics and Gynecology, Kantonsspital, Münsterlingen, Switzerland; *Department of Obstetrics and Gynecology, University of Insubria, Varese, Italy; †Department of Obstetrics and Gynecology, University of Bari, Italy; and ‡Department of Obstetrics and Gynecology, Ben Gurion University, Beer-Sheva, Israel

ABSTRACT

Objective *The purpose of this study was to investigate whether the prenatal diagnosis of a 'lean' umbilical cord in otherwise normal fetuses identifies fetuses at risk of being small for gestational age (SGA) at birth and of having distress in labor. The umbilical cord was defined as lean when its cross-sectional area on ultrasound examination was below the 10th centile for gestational age.*

Method *Pregnant women undergoing routine sonographic examination were included in the study. Inclusion criteria were gestational age greater than 20 weeks, intact membranes, and singleton gestation. The sonographic cross-sectional area of the umbilical cord was measured in a plane adjacent to the insertion into the fetal abdomen. Umbilical artery Doppler waveforms were recorded during fetal apnea and fetal anthropometric parameters were measured.*

Results *During the study period, 860 patients met the inclusion criteria, of whom 3.6% delivered a SGA infant. The proportion of SGA infants was higher among fetuses who had a lean umbilical cord on ultrasound examination than among those with a normal umbilical cord (11.5% vs. 2.6%, p < 0.05). Fetuses with a lean cord had a risk 4.4-fold higher of being SGA at birth than those with a normal umbilical cord. After 25 weeks of gestation, this risk was 12.4 times higher when the umbilical cord was lean than when it was of normal size. The proportion of fetuses with meconium-stained amniotic fluid at delivery was higher among fetuses with a lean cord than among those with a normal umbilical cord (14.6% vs. 3.1%, p < 0.001). The proportion of infants who had a 5-min Apgar score < 7 was higher among those who had a lean cord than among those with normal umbilical cord (5.2% vs. 1.3%, p < 0.05). Considering only patients admitted in labor with intact membranes and who delivered an appropriate-for-gestational-age infant, the proportion of fetuses who had oligohydramnios at the time of delivery was higher among those who had a lean cord than among those with a normal umbilical cord (17.6% versus 1.3%, p < 0.01).*

Conclusion *We conclude that fetuses with a lean umbilical cord have an increased risk of being small for gestational age at birth and of having signs of distress at the time of delivery.*

INTRODUCTION

Little is known about the function, formation and deposition of Wharton's jelly. Pathological studies and case reports have demonstrated that a thin umbilical cord is associated with adverse pregnancy outcome[1–5]. Labarrere and colleagues have described an association between a reduced amount of Wharton's jelly and fetal or neonatal death when the length and insertion of the umbilical cord at the placental site were normal in the absence of known risk factors for fetal or neonatal death[6]. The reduced amount of Wharton's jelly may be the result of an inherited disorder in the deposition of Wharton's jelly, making the umbilical circulation vulnerable to insults rather than the consequence of fetal disease *per se*. Indeed, successive fetal deaths in the same family due to a torsion of the umbilical cord as the consequence of primary absence of Wharton's jelly have been previously described[7].

A lean umbilical cord at birth has also been associated with oligohydramnios and fetal distress. Silver and colleagues[8] have reported that, in post-term pregnancies, the diameter of the umbilical cord is smaller in patients

Correspondence: Dr L. Raio, Kantonsspital Münsterlingen, Department of Obstetrics and Gynecology, CH 8596 Münsterlingen, Switzerland

with oligohydramnios than in those with normal amniotic fluid. In addition, these authors found a higher incidence of variable decelerations antepartum in patients with a small umbilical cord diameter than in those with a normal umbilical cord.

Moreover, isolated cases of thin umbilical cord associated with small-for-gestational-age (SGA) infants have been described by several authors[1,9,10]. Using computerized microscope morphometry, it has been recently demonstrated that growth-restricted fetuses have a lower amount of Wharton's jelly at birth than normal healthy fetuses[10].

The purpose of this study was, first, to investigate whether the prenatal diagnosis of a lean umbilical cord in otherwise normal fetuses identifies fetuses at risk for being SGA at delivery and, second, to explore the relationship existing between the prenatal size of the umbilical cord and the occurrence of fetal distress in labor.

METHODS

The study population consisted of pregnant women admitted consecutively to the Obstetrics and Gynecologic Department of Münsterlingen Kantonsspital, Switzerland, between May 1995 and July 1997. Inclusion criteria were singleton gestation, gestational age greater than 20 weeks, intact membranes, normal Doppler flow velocimetry of the umbilical artery at the time of ultrasound, and known gestational age. Patients were excluded if, at the time of ultrasound, at least one of the following conditions was present: detectable structural anomalies, pregnancy complications (i.e. diabetes, hypertensive disorders, previous delivery of a SGA infant), estimated fetal weight below the 10th centile for gestational age[11], and amniotic fluid index < 5 cm or > 25 cm[12]. Gestational age was determined by a reliable recollection of the last menstrual period and by an ultrasonographic examination before 20 weeks of gestation. The sonographic cross-sectional area of the umbilical cord was measured in a plane adjacent to the insertion into the fetal abdomen using the software of the ultrasound machine (Figure 1). Intra- and interobserver variabilities were 4.3% and 5.1%, respectively[13]. Doppler flow velocity waveforms of the umbilical artery were recorded during

Figure 1 Ultrasonographic measurement of the area of the umbilical cord

fetal apnea and, when at least three consecutive waveforms showing a consistent pattern were obtained, the pulsatility index was calculated. Each patient was included only once. Fetal anthropometric parameters including biparietal diameter, abdominal circumference and femur length were measured in all fetuses and the estimated fetal weight calculated. The amniotic fluid index was measured in all patients who were subsequently admitted with intact membranes in labor. All ultrasound examinations were performed with a Toshiba SSH-140A unit (Toshiba Corporation, Medical Systems Division, Tokyo, Japan) equipped with a 3.75-MHz transducer. All placentas were weighed at the time of delivery.

The newborns were considered small for gestational age when the birth weight was below the 5th centile according to the gestational age at delivery[14]. Delivery was considered as preterm when it occurred before 37 weeks of gestation. Meconium-stained amniotic fluid was considered to be present when it was greenish, opaque, and not watery, with visually identifiable particulate matter. An umbilical cord was defined as lean when its cross-sectional area was below the 10th centile for gestational age[15]. This study was approved by the Human Research Review Committee.

Statistical analysis

Statistical analysis was performed using Stat view 4.1 (Abacus Concepts Inc, Berkeley, CA, USA). The Mann–Whitney U test or Student t test was used for comparison of continuous variables and proportions were analyzed using the Fisher exact or χ^2 test. The Spearman rank correlation was used to correlate characteristics of intrauterine vessels with placental weight and birth weight. Statistical significance was considered achieved when p was less than 0.05.

RESULTS

During the study period, 860 patients met the inclusion criteria. The prevalence of SGA infants was 3.6% (31/860). Table 1 shows the patient characteristics according to the umbilical cord area. The proportion of SGA infants was higher among fetuses who had a lean umbilical cord on ultrasound examination than among those with a normal umbilical cord (11/96 (11.5%) vs. 20/764 (2.6%), $p < 0.05$). Figure 2 displays the values of the umbilical cord area in the SGA infants. The diagnostic indices of the presence of a lean cord in the detection of fetuses at risk of being SGA at delivery were the following: sensitivity 35.5% (11/31), specificity 89.7% (744/829), positive and negative predictive values 11.5% (11/96) and 97.4% (744/764), respectively. Patients with a lean umbilical cord had a 4.4-fold higher risk (95% confidence intervals 2.16–8.85) of having an SGA infant than those with a normal umbilical cord. If we restrict the analysis to women who underwent an ultrasound examination at or after 25 weeks of gestation ($n = 678$), the risk of having a SGA infant was 12.4-fold higher (95% confidence interval 4.37–34.67) when the umbilical cord was lean than when it

Table 1 Clinical characteristics of the study population according to the umbilical cord area

Characteristics	Lean umbilical cord (n = 96)	Normal umbilical cord (n = 764)	Significance
Maternal age (mean ± SD) (years)	28.3 ± 5.6	28.5 ± 4.7	NS
Gestational age at ultrasound (mean ± SD) (weeks)	32.9 ± 5.8	31.3 ± 6.05	$p < 0.05$
Gestational age at delivery (mean ± SD) (weeks)	39.4 ± 2	39.6 ± 1.1	NS
Interval examination-to-delivery (median, range) (days)	61 (0–147)	70 (0–154)	NS
Nulliparous (n, %)	36 (37.5%)	198 (25.9%)	NS
Smoking habit (n, %)	27 (28.1%)	151 (19.7%)	NS
Cesarean deliveries (n, %)	18 (18.7%)	70 (9.2%)	$p < 0.01$
Birth weight (mean ± SD) (g)	3018 ± 539	3430 ± 477	$p < 0.01$
Placental weight (mean ± SD) (g)	524 ± 124	596 ± 127	$p < 0.01$

NS, not significant
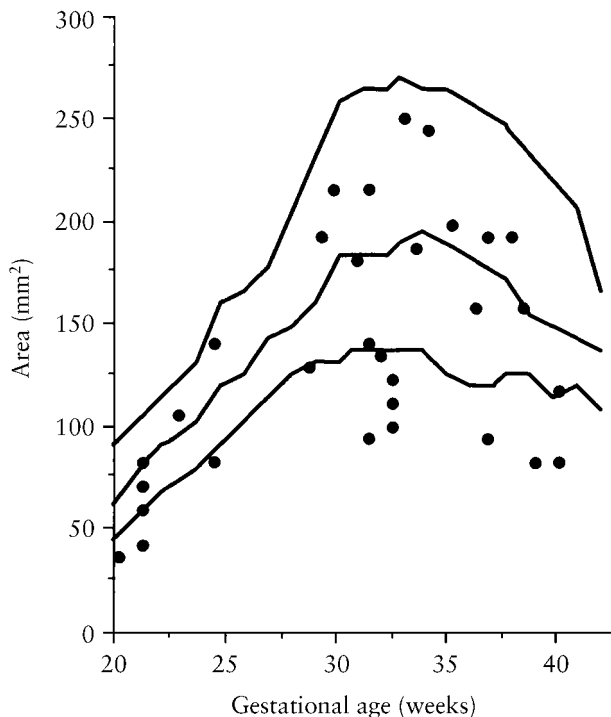
Figure 2 Antenatal values of the area of the umbilical cord of small-for-gestational-age infants plotted on the reference range[15]. The lines represent the 10th, 50th and 90th centiles for gestational age

was of normal size, and the diagnostic indices were: sensitivity 34.8% (8/23), specificity 95.9% (628/655), positive and negative predictive values 22.9% (8/35) and 97.7% (628/643), respectively.

To further explore the clinical significance of a lean umbilical cord, we analyzed the association between the antenatal cross-sectional area of the umbilical cord and the occurrence of meconium-stained amniotic fluid, low Apgar score and oligohydramnios. The proportion of fetuses with meconium-stained amniotic fluid at delivery was higher among fetuses with a lean cord on ultrasound examination than among those with a normal umbilical cord (14/96 (14.6%) vs. 24/764 (3.1%), $p < 0.001$). The number of infants who had a 5-min Apgar score less than 7 was higher among those who had had a lean cord than among those with a normal umbilical cord (5/96 (5.2%) vs. 10/764 (1.3%), $p < 0.05$). Excluding patients who delivered a SGA

infant and those whose membranes ruptured, the proportion of patients who had oligohydramnios at the time of delivery was higher among fetuses with a lean umbilical cord on ultrasound examination than among those who had a normal umbilical cord (12/68 (17.6%) vs. 8/595 (1.3%), $p < 0.01$). No difference was found in the proportion of fetuses with a lean umbilical cord between male and female infants (43/417 males vs. 53/443 females).

To investigate the relationship between the presence of a lean umbilical cord antenatally and infant and placental characteristics, we considered patients who had an ultrasound examination after 32 weeks of gestation (n = 403). The analysis was restricted to this group of patients because the cross-sectional area of the umbilical cord does not change as a function of gestational age between 32 and 42 weeks of gestation (Figure 2). A significant correlation was found between the antenatal cross-sectional area of the umbilical cord and placental weight ($r = 0.52$, $p < 0.01$) and birth weight ($r = 0.37$, $p < 0.01$). For those 84 patients where the length of the umbilical cord was available, no correlation was found between the antenatal cross-sectional area and the length of the umbilical cord.

DISCUSSION

A Medline search of the literature from 1966 onward was performed to identify studies on measurements of the umbilical cord and adverse pregnancy outcome. This is the first study to investigate the relationship between the prenatal size of the umbilical cord and the delivery of a SGA infant and it is the largest report to correlate the antenatal size of the umbilical cord with the occurrence of signs of fetal distress, such as meconium-stained amniotic fluid, low Apgar score and oligohydramnios.

The most important finding of this study is that a significant proportion of SGA infants have a lean umbilical cord during intrauterine life and that this is detectable on ultrasound examination. Bruch and colleagues[10] have reported that intrauterine growth-restricted (IUGR) fetuses with or without Doppler abnormalities of the umbilical arteries have a smaller cross-sectional area of the umbilical cord at delivery than normal healthy fetuses. These authors found that IUGR fetuses with normal Doppler waveforms of the umbilical arteries have a reduction in the total umbilical cord area when compared to that of healthy infants.

However, no modifications were observed in the total lumen area of both arteries, suggesting that the difference in the cross-sectional area of the umbilical cord between IUGR and normal fetuses is mainly due to diminution of Wharton's jelly and umbilical vein reduction. The smaller amount of Wharton's jelly may be the consequence of either an extracellular dehydration or a reduction in extracellular matrix component. It has been proposed that Wharton's jelly cushions umbilical blood vessels, preventing disruption of flow due to compression or bending caused by fetal movements and uterine contraction at delivery[16]. Wharton's jelly appears to serve the function of adventitia, which the umbilical cord lacks, binding and encasing the umbilical vessels. It has been speculated that the cells of Wharton's jelly may participate in the regulation of umbilical blood flow and that, at least in some cases, the reduction in fetal growth could be the consequence of diminution of Wharton's jelly leading to vascular hypoplasia of the umbilical vessels[10,17]. In fact, a reduction in wall thickness of umbilical cord arteries and vein has been found in IUGR infants with abnormal umbilical artery flow when compared to IUGR infants without increased umbilical artery resistance[9]. Therefore, it can be hypothesized that the greater the reduction in the amount of Wharton's jelly, the greater the damage to the umbilical cord vessels and the greater the compromise to the growth of the fetus.

The second important observation of the present study is that a lean umbilical cord is more frequently associated with signs of fetal distress at the time of delivery (oligohydramnios, low Apgar score and meconium-stained amniotic fluid). This is in agreement with the study by Silver and colleagues[8] who found an association between a small diameter of the umbilical cord and the presence of oligohydramnios and/or variable deceleration at the time of delivery in post-term pregnancy. These authors have also described a significant association between prenatal umbilical cord diameter and the amount of amniotic fluid. Previous studies have shown that the water content of Wharton's jelly decreases progressively in late gestation[17] and that the water content is significantly correlated with the amount of Wharton's jelly as measured by cord circumference[18]. A bidirectional transfer of water and metabolites between amniotic fluid and umbilical cord vessels through the Wharton's jelly has been demonstrated[19,20]. Of note, Goodlin[1] reported an association between a lean umbilical cord after delivery and the presence of oligohydramnios and meconium-stained amniotic fluid in five cases of emergency Cesarean sections performed for fetal distress (scalp pH < 7.20). In all these cases, there was essentially no Wharton's jelly around the umbilical arteries and little around the umbilical vein. Moreover, modifications in the amount and composition of Wharton's jelly have been described in a number of pathological conditions, usually associated with modification of the amniotic fluid volume, occurring in pregnancy (i.e. hypertensive disorders[21], gestational diabetes[22]). Collectively, these findings and the reduction of water content with the increase in gestational age strongly suggest a metabolically active role for the umbilical cord[19]. Considering that all fetuses included in our study had a normal amount of amniotic fluid at the time of ultrasound examination, it seems that the presence of a lean umbilical cord is a condition that precedes the reduction of amniotic fluid.

We believe that the antenatal measurement of the umbilical cord area is probably a better parameter than determination of the umbilical cord diameter to identify fetuses at risk of being small for gestational age at delivery or of having distress in labor, because it has been demonstrated that, in the case of segmental thinning of the umbilical cord, the greater reduction of Wharton's jelly occurs especially around the umbilical arteries[1,6]. Thus, considering that the cross-sectional shape of the umbilical cord may not be perfectly circular, minimal reduction of Wharton's jelly without modification of the arterial lumen could be underestimated with only the evaluation of the umbilical cord diameter.

Another interesting finding of this study is that there is a correlation between umbilical cord area and birth weight. This is in accordance with a previous study by Prabhcharan and Jarjoura[23] who reported a significant relationship between the quantity of Wharton's jelly and neonatal birth weight. Moreover, a correlation between the content of Wharton's jelly, umbilical cord diameter and estimated fetal weight has been reported in non-macrosomic fetuses of mothers diagnosed as having gestational diabetes[22].

A limitation of this study is that it was conducted in a population at low risk for fetal growth restriction and, therefore, the most severe forms of intrauterine growth- restricted fetuses could not be investigated. However, Minior and Divon[24] have recently reported that a small-for-gestational-age newborn from an uncomplicated pregnancy delivered at term has increased neonatal morbidity compared with its appropriate-for-gestational age counterparts.

Since the umbilical cord area is easy to measure and nomograms are now available, we suggest that the measurement of umbilical cord area could be part of a routine ultrasound evaluation and should prompt the physician to carefully evaluate the case whenever there is a discrepancy between the observed and the normal values.

REFERENCES

1. Goodlin RC. Fetal dysmaturity, 'lean cord', and fetal distress. *Am J Obstet Gynecol* 1987;56:716
2. Hall PK. The thin cord syndrome. A review with a report of two cases. *Obstet Gynecol* 1961;118:507–9
3. Sun Y, Arbuckle S, Hocking G, Billson V. Umbilical cord stricture and intrauterine fetal death. *Pediatr Pathol Lab Med* 1995;5:723–32
4. Qureshi F, Jacques SM. Marked segmental thinning of the umbilical cord vessels. *Arch Pathol Lab Med* 1994;118:826–30
5. Clausen I. Umbilical cord anomalies and antenatal fetal deaths. *Obstet Gynecol Surv* 1989;44:841–5
6. Labarrere C, Sebastiani M, Siminovich M, Torassa E, Althabe O. Absence of Wharton's jelly around the umbilical arteries: an unusual cause of perinatal mortality. *Placenta* 1985;6:555–9

7. Hersh J, Buchino JJ. Umbilical cord torsion/constriction sequence. In Saul RA, ed. *Proceedings of the Greenwood Genetics Conference*, Vol. 7. Clinton: Jacobson Press, 1988: 181–2

8. Silver RK, Dooley SL, Tamura RK, Depp R. Umbilical cord size and amniotic fluid volume in prolonged pregnancy. *Am J Obstet Gynecol* 1987;157:716–20

9. Scott JM, Wilkinson R. Further studies on the umbilical cord and its water content. *J Clin Pathol* 1978;31:944–8

10. Bruch JF, Sibony O, Benali K, Challer C, Blot P, Nessmann C. Computerized microscope morphometry of umbilical vessels from pregnancies with intrauterine growth retardation and abnormal umbilical artery Doppler. *Hum Pathol* 1997;28: 1139–45

11. Hadlock FP, Harrist RB, Carpenter RJ, Deter RL, Park SK. Sonographic estimation of fetal weight: the value of femur length in addition to head and abdomen measurements. *Radiology* 1984;150:535–40

12. Phelan JP, Vernon Smith C, Broussard P, Small M. Amniotic fluid volume assessment with the four quadrant technique at 36–42 weeks' gestation. *Obstet Gynecol* 1987;32:540–2

13. Raio L, Ghezzi F, Di Naro E, Gomez R, Saile G, Brühwiler H. The clinical significance of antenatal detection of discordant umbilical arteries. *Obstet Gynecol* 1998;91:86–91

14. Largo RH, Walli R, Duc G, Fanconi A, Prader A. Evaluation of perinatal growth. Presentation of combined intra- and extrauterine growth standards for weight, length and head circumference. *Helv Paediatr Acta* 1980;35:419–36

15. Raio L, Ghezzi F, Di Naro E, Gomez R, Franchi M, Mazor M, Brühwiler H. Sonographic measurements of the umbilical cord and fetal anthropometric parameters. *Eur J Obstet Gynecol Reprod Biol* 1999;in press

16. Takechi K, Kuwabara Y, Mizuno M. Ultrastructural and immunohistochemical studies of Wharton's jelly umbilical cord cells. *Placenta* 1993;14:235–45

17. Gebrane-Younes J, Minh HN, Orcel L. Ultrastructure of human umbilical vessels: a possible role in amniotic fluid formation? *Placenta* 1986;7:173–85

18. Weissman A, Jakobi P, Bronshtein M, Goldstein I. Sonographic measurements of the umbilical cord and vessels during normal pregnancies. *J Ultrasound Med* 1994;13:11–14

19. Sloper KS, Brown RS, Baum JD. The water content of the human umbilical cord. *Early Hum Dev* 1979;3:205–10

20. Vizza E, Correr S, Goranova V, Heyn R, Angelucci PA, Forleo R, Motta PM. The collagen skeleton of the human umbilical cord at term. A scanning electron microscopy study after 2N-NaOH maceration. *Reprod Fertil Dev* 1996;8:885–94

21. Bankowski E, Sobolewski K, Romanowicz L, Chyczewski L, Jawosrski S. Collagen and glycosaminoglycans of Wharton's jelly and their alterations in EPH-gestosis. *Eur J Obstet Gynecol Reprod Biol* 1996;66:109–17

22. Weissman A, Jakobi P. Sonographic measurements of the umbilical cord in pregnancies complicated by gestational diabetes. *J Ultrasound Med* 1997;16:691–4

23. Prabhcharan G, Jarjoura D. Wharton's jelly in the umbilical cord. A study of its quantitative variations and clinical correlates. *J Reprod Med* 1993;38:612–14

24. Minior VK, Divon MY. Fetal growth restriction at term: myth or reality? *Obstet Gynecol* 1998;92:57–60