Gestational diabetes mellitus: the correlation between umbilical coiling index, and intrapartum as well as neonatal outcomes

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Abstract

Objectives The objective of this study was to investigate the relationship between the postnatal umbilical coiling index (pUCI), and intrapartum and neonatal outcomes in parturients with gestational diabetes mellitus (GDM) and non-GDM.

Methods An evaluation of the umbilical cords and pUCI of 117 neonates of GDM and 105 of non-GDM parturients were prospectively studied within 24 h after delivery. Furthermore, obstetric history, intrapartum and neonatal data were recorded.

Results Premature rupture of membrane (PROM) ($p = 0.001$), emergency cesarean delivery ($p = 0.01$), spontaneous preterm delivery ($p = 0.006$), duration of hospital admission ($p < 0.001$), and congenital malformations ($p = 0.03$) were significantly higher in the GDM group. Moreover, pUCI had a significant association with large for gestational age (LGA) ($p = 0.009$), and meconium-stained amniotic fluid ($p = 0.04$) in the GDM group. In addition, increment of pUCI had significant association with spontaneous preterm delivery in both groups ($p = 0.002$) (OR = 1.23).

Conclusions GDM is associated with spontaneous preterm delivery, PROM, emergency cesarean delivery, duration of hospital admission, and congenital malformations. Increase in pUCI could increase the rate of spontaneous preterm delivery in normal pregnancy and pregnancy complicated by GDM, as well as, the rate of LGA and meconium-stained amniotic fluid in GDM.

Keywords Intrapartum outcomes · Neonatal outcomes · Postnatal · Umbilical coiling index · Gestational diabetes mellitus

Abbreviations

GA Gestational Age
GDM Gestational Diabetes Mellitus
LGA Large for gestational age

NICU Neonatal intensive care unit
PROM Premature rupture of membranes
pUCI Postnatal Umbilical Coiling Index
UCI Umbilical Coiling Index

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Introduction

The umbilical cord is the vital lifeline of the fetus and cord abnormalities can lead to fetal morbidity and mortality [1].

The standard method currently used to quantify the degree of umbilical vascular coiling is the umbilical coiling index (UCI) [2], and the changes of UCI is individualized [3].

Several studies have shown the correlations between coiling abnormalities and adverse fetal outcomes such as intrauterine fetal death, fetal chromosomal abnormalities, intrauterine growth retardation, low Apgar score, preterm delivery and respiratory distress during labour [2, 4–7]. However, these results are ambivalent in several aspects. The correlation between adverse fetal outcomes and UCI is not confirmed and is controversial between different studies. The cause of abnormal coiling is unknown [4]. The abnormalities of UCI could induce abnormal flow, constriction or thrombosis in the umbilical cord which may cause adverse perinatal outcomes [4]. One of the most important risk factors for abnormal vascular coiling of the umbilical cord is gestational diabetes mellitus (GDM) [5] which has a injurious effect on the connective tissue components of the Wharton's jelly and the umbilical vessels [8]. Vascular wall or connective tissue is the most important etiology in the perinatal mortality and morbidity increment in the GDM [8]. Recent studies have demonstrated that even in the presence of optimal glycemic control, placental changes and stillbirth may still occur [9]. Simple differences in mechanical properties of the cord are not the only reasons for the correlation between coiling abnormalities and adverse perinatal outcomes. It can also be explained by growth response of the cord to metabolic and pharmacological abnormalities as well as intrinsic vascular structural changes. In addition, variations in placental morphology affecting placental blood flow and maternal-fetal gas exchange are the other reasons [10, 11].

Considering the impact of UCI on fetal outcomes, the aim of the present study was to explore the association between postnatal umbilical coiling index (pUCI) and adverse intrapartum and neonatal outcomes in GDM and non-GDM pregnancy.

Materials and methods

Subjects

In this prospective cohort study we analyzed the data from a longitudinal cohort of parturients comprised of gestational diabetes mellitus and non-gestational diabetes pregnancy [12] during April 18th, 2015, till November 8th, 2016.

The study was performed on 310 consecutive and unselected singleton parturients. The parturients were recruited at the 13th week of gestation (determined by the first day of the last

menstrual period or 1st trimester ultrasound scan using crown-rump length) and followed till delivery and postpartum period. The sample size was calculated by G power software (version 3.1), power = 90%, $\alpha = 5\%$ and the correlation of fetal outcomes (LGA, small for gestational age, spontaneous preterm delivery and PROM) and coiling index [1].

The exclusion criteria were overt diabetes, presence of gross fetal anomalies, history of chronic hypertension, abortion, smoking or substance abuse, systemic disease, use of medications other than routine pregnancy supplements, single-artery umbilical cord, and multifetal pregnancy.

Face to face interview was performed in the first and the following prenatal visits by a trained physician. Maternal and fetal anthropometric variables and paraclinic parameters were collected from the patient's files.

Gestational diabetes was diagnosed according to the American Diabetes Association criteria at 24 to 28 weeks of gestation using one-step strategy [13–15].

Macroscopic assessment

Macroscopic examination of placenta and umbilical cord carried out in accordance with previously published protocols [16]. A true pUCI was grossly evaluated within 24 h after delivery and cord clamping in the fresh state by a trained single physician who was blinded to the parturients' characteristics, and pregnancy outcomes. Immediately after birth both placental and fetal ends of the cord was clamped and cut straight at five cm from the fetal insertion taking care not to milk and stretch the cord (which may affect the UCI). Five centimeters was added to the length of each cord, to account for the portion of the cord that remained attached to the fetal umbilicus [17]. The length of the umbilical cord was measured against a non-elastic tape graduated in centimeters, from its insertion into the placenta up to neonatal clamp. The placenta was allowed to separate spontaneously. Immediately after delivery, the placenta and the umbilical cord were preserved in a labeled, clean and dry plastic container full of normal saline [18] with an airtight lid. They were kept in a dry, clean laboratory with constant temperature maintained at 5 °C and were washed clean of blood before examination. The umbilical cord attachment to the placenta was examined; one coil defined as complete 360 degrees of umbilical artery around umbilical vein. The pUCI was determined by dividing the total number of complete umbilical cord twists by the total umbilical cord length in centimeters resulting in a range variability (0–1).

Intrapartum and neonatal outcomes

Intrapartum outcomes included gestational age at delivery, emergency cesarean delivery, premature rupture of membranes (PROM), polyhydramnios, and meconium staining of amniotic fluid. PROM was defined as rupture of the membrane more than

1 h before the onset of labor. Polyhydramnios was defined as an excess of amniotic fluid index greater than 24 cm expected for gestational age in the amniotic sac. Meconium staining of amniotic fluid included the presence of any degree and concentration of the meconium in the amniotic fluid noticed during delivery.

Neonatal outcomes were examined by a pediatrician in all cases after delivery, who was blinded about the maternal and macroscopic evaluation. Neonatal outcomes included first minute Apgar score, respiratory distress syndrome, neonatal hypoglycemia, neonatal intensive care unit (NICU) admission, fetal complications (congenital anomalies / malformations and perinatal / newborn complications), large for gestational age (LGA), small for gestational age and preterm delivery.

Immediate neonatal morbidity includes first minute Apgar score, respiratory distress syndrome, neonatal hypoglycemia [19], and NICU admission. Fetal complications was categorized as congenital anomalies / malformations (congenital heart disease, limb defects, club foot, hypospadias, undescended testis, cleft palate, Down syndrome, hypothyroidism, pitting of coccyx area, skin manifestations, frenulum of tongue, umbilical hernia), and perinatal / newborn complications (neonatal jaundice [19], hip dislocation, Caput Succedaneum, sepsis, meconium aspiration syndrome, transient tachypnea of the newborn) were evaluated later. LGA was defined as birth weight > the 90th percentile for the gestational age. Small for gestational age was defined as birth weight < the 10th percentile for the gestational age [20]. Preterm delivery was defined as delivery before 37 weeks of gestation.

The study protocol was approved by the local ethical committee of Iran University of medical sciences (IR.IUMS.REC.1393 .24991) and the written informed consent was signed by all the parturients.

Statistical analysis

Statistical analysis was performed using SPSS (version 16, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to assess the baseline characteristics (means (SE) and proportions). For the continuous variables (including demographics, intrapartum, and neonatal outcomes) with normal distributions, independent sample t-test was used to compare the GDM and non-GDM groups. Also, for the covariates with less than 30 observations, non-parametric Mann-Whitney U test was utilized. In the next step, those responses which showed significant differences between the two groups were put in logistic regression model. Moreover, other clinically remarkable events, which were not significant in the t-test step, were also assessed using the logistic regression.

An indicator variable for comparing the GDM and non-GDM groups, and the UCI value were put as the covariates in the regression model. A *p* value of .05 was considered significant.

Results

In the study period 310 parturients were enrolled. Eighty eight were excluded due to loss to follow-up. In the present study, 222 parturients recruited with complete macroscopic parameters and neonatal outcome variables, 117 parturients were included in the GDM group and 105 in the non-GDM group, the missing rate of all measured variables were lower than 5%.

Demographic and reproductive characteristics of the parturients are summarized in Table 1.

The frequency distribution of the pUCI (10th, 90th percentiles and mean (SE)) in GDM and non-GDM groups were (0.10, 0.36, 0.21(0.01)) coils/cm and (0.10, 0.32, 0.21(0.008)) coils/cm, respectively (*p* value = 0.61).

Table 2 compares the intrapartum and neonatal outcomes of the parturients according to diagnosis (GDM, non-GDM).

In the GDM group, the mean (SE) of neonatal blood sugar was 59.58 (0.77), and 1.7% of the neonates experiencing neonatal hypoglycemia (i.e. the blood sugar lower than 40 mg/dl, in term and preterm at 2 h after delivery).

Table 3 compares the pUCI between levels of intrapartum and neonatal outcomes, separated for 2 groups.

The box-plots for the significant outcomes were illustrated in the [supplementary files](#) for description of pUCI values. According to Table 3, in the GDM group, the pUCI mean was significantly higher for those who were LGA and meconium-stained amniotic fluid. Despite the mentioned significance, we are aware of the issue of simultaneous multiple comparisons, thus we do not emphasize on these differences. Indeed, these intrapartum and neonatal outcomes have some clinical importance for the authors regardless of the mentioned borderline significance.

Thus, these two binary outcomes were put in logistic regression models, using the pUCI score as the covariate. The results showed no significant differences.

The binary logistic regression models were fitted to explore association of intrapartum and neonatal outcomes with pUCI, in the presence of the GDM/non-GDM indicator (with the non-GDM as the reference) (Table 4). The odds ratios were evaluated according to 0.05 unit change in pUCI.

Adjusting for pUCI, the odds ratio of spontaneous preterm delivery, PROM, emergency cesarean delivery, duration of hospital admission and congenital malformations for GDM group were 3.98, 3.40, 2.48, 3.99 and 2.83 times, in comparison with non-GDM group, respectively.

On the other hand, 0.05 unit increment of pUCI value was associated with spontaneous preterm delivery (OR = 1.23). The mean of gestational age for spontaneous preterm delivery in overall, normal and GDM parturients were as follows: 36.02 ± 0.22 , 36.07 ± 0.45 and 36 ± 0.25 weeks, respectively; no significant difference was detected between studied groups (*P* = 0.87).

Table 1 Demographic and reproductive characteristics of the parturients

	GDM [†] (N = 117)	Non-GDM(N = 105)	p value
Maternal age (yrs., mean(SE))	31(0.48)	28.1(0.55)	<0.001
Gravidity (median (IQ))	2(2,3)	2(1,3)	0.86
Parity (median (IQ))	1(0,2)	1(0,1)	0.93
History of Abortion (n (%))	27(23.1)	22(21)	0.7
History of stillbirth (n (%))	5(4.3)	3(2.9)	0.72
History of macrosomia (n (%))	8(6.8)	1(1)	0.03
History of GDM (n (%))	19(16.2)	3(2.9)	0.001
Family history of diabetes mellitus (n (%))	46(39.3)	14(13.3)	<0.001
Pre-pregnancy body mass index (mean(SE))	26.9(0.33)	25.6(0.41)	0.01
Preeclampsia (n (%))	29(25)	9(8.7)	0.002
Eclampsia (n (%))	2(1.7)	0(0)	0.49
Average of GA [‡] at enrollment(mean(SE))	17.09 (0.33)	17.60 (0.30)	0.60
Average of GA at delivery time(mean(SE))	37.68 (0.14)	38.44 (0.15)	0.002

[†] GDM Gestational diabetes mellitus. [‡]GA Gestational age

Statistical analysis: data are expressed as mean (SE) (Standard error), Median (IQ) (Interquartile) and n (%) (Number (%))

In this study, in another logistic regression model, the baseline and demographic characteristics were adjusted in presence of pUCI and GDM/non-GDM groups that no significant association was detected. Furthermore, we analyzed the pUCI categorization (hypocoiling, normocoiling, hypercoiling and noncoiling [12]) status by multivariate logistic regression model; pUCI categorization was not significantly associated with intrapartum or neonatal outcomes. Moreover, interaction terms were considered in all the regression models and no significant interaction was found.

Discussion

In the present study, the pUCI increment was correlated with LGA and meconium-stained amniotic fluid in the GDM group. Moreover, increase in pUCI value could increase the chance of spontaneous preterm delivery by 1.23 folds. On the other hand, pUCI categorization [12] was not correlated with intrapartum or neonatal outcomes.

The strengths of the study include comparison of gestational diabetes mellitus and normal pregnancy. In addition, the

Table 2 Comparison of the intrapartum and neonatal outcomes, between the GDM/non-GDM groups

Outcomes	GDM [†] (N = 117)	Non- GDM [†] (N = 105)	p value
PROM [‡] (n (%))	22 (18.8)	4 (3.8)	0.001
Polyhydramnios (n (%))	21 (17.9)	12 (12.2)	0.17
Meconium-stained amniotic fluid (n (%))	9 (7.8)	9 (8.7)	0.06
Emergency cesarean delivery (n (%))	26 (22.2)	10 (9.5)	0.01
Apgar score (1 min) (mean(SE))	8.68 (0.85)	8.62 (1.09)	0.615
Large for gestational age infants (n (%))	7 (6)	3 (3)	0.34
Small for gestational age infants (n (%))	6 (5.1)	3 (3)	0.50
Spontaneous preterm delivery (n (%))	26 (22.2)	9 (8.7)	0.006
Clinical fetal distress (n (%))	12 (10.3)	13 (12.7)	0.47
NICU [§] admission (n (%))	5 (4.3)	1 (0.9)	0.22
Hospital admission (days (median(IQ))	1 (1,2)	0 (0,2)	<0.001
Congenital malformations (n (%))	17 (14.5)	6 (5.7)	0.03
Newborn complications (n (%))	44 (37.6)	32 (30.5)	0.26

[†] GDM Gestational diabetes mellitus, [‡]PROM Premature rupture of membrane, [§]NICU Neonatal intensive care unit

Statistical analysis: data are expressed as n (%) (Number (%)), mean (SE) (Standard error) and Median (IQ) (Interquartile)

Table 3 The comparison of pUCI between levels of intrapartum and neonatal outcomes, separated for GDM/ non-GDM groups

Outcomes	GDM [‡]	Mean pUCI [†]		
		<i>p</i> value	Non-GDM	<i>p</i> value
Apgar score (1 min) (<7, ≥7)	0.24,0.21	0.46	0.21,0.20	0.61
Polyhydramnios (No,Yes)	0.21,0.20	0.91	0.20,0.21	0.94
Large for gestational age (No,Yes)	0.20,0.29	0.009*	0.20,0.18	0.76
Spontaneous preterm delivery (No,Yes)	0.21,0.21	0.66	0.20,0.17	0.36
PROM [§] (No,Yes)	0.21,0.20	0.83	0.20,0.26	0.46
Meconium-stained amniotic fluid (No,Yes)	0.20,0.27	0.04*	0.20,0.21	0.52
Emergency cesarean delivery (No,Yes)	0.21,0.20	0.64	0.20,0.21	0.19
Clinical fetal distress (No,Yes)	0.21,0.18	0.48	0.20,0.23	0.36
NICU [§] admission (No,Yes)	0.21,0.16	0.26	0.20,0.18	0.94
Hospital admission (≤1,>1 days)	0.21,0.21	0.88	0.21,0.19	0.55
Congenital malformations (No,Yes)	0.21,0.23	0.70	0.20,0.22	0.49
Newborn complications (No,Yes)	0.20,0.23	0.14	0.20,0.21	0.15

[†]*pUCI* Postnatal umbilical coiling index, [‡]*GDM* Gestational diabetes mellitus, [§]*PROM* Premature rupture of membrane, [§]*NICU* Neonatal intensive care unit

Data are expressed as mean for the categories of variables in each group

Statistical analysis: t-test

*A *p* value of .05 was considered significant

**

measurement pathway considered the total length of the cord to calculate UCI. Moreover, rapid bilateral clamping of the cord was done to avoid urgent drainage of the blood. However, we did not consider the effect of preeclampsia/eclampsia on the adverse fetomaternal outcomes. Using “one-step” 75-g oral glucose tolerance test for gestational

diabetes diagnosis may be a limitation of the present study which causes over diagnosis and confounding our results.

Previous studies have noted that coiling abnormalities are correlated with poor perinatal outcomes in uncomplicated pregnancies [1, 2, 5, 21–23]. However, the association shows wide variations among the studies.

Table 4 Logistic regression analysis of intrapartum and neonatal outcomes, for assessing the role of pUCI and group indicator (GDM or non-GDM)

Outcomes	pUCI [†]		GDM/non-GDM	
	Odds ratio	[95% CI.]	Odds ratio	[95% CI.]
Apgar score (1 min) (<7, >7)	1.07	0.92–1.25	1.57	0.71–3.48
Spontaneous preterm delivery (No,Yes)	1.23*	1.07–1.41	3.98*	1.66–9.54
PROM [‡] (No,Yes)	1.001	0.84–1.17	3.40*	1.30–8.92
Meconium-stained amniotic fluid (No,Yes)	1.004	0.84–1.19	0.88	0.33–2.33
Emergency cesarean delivery (No,Yes)	0.87	0.75–1.01	2.48*	1.12–5.49
Clinical fetal distress (No,Yes)	0.96	0.82–1.12	0.75	0.32–1.74
NICU [§] admission (No,Yes)	0.97	0.69–1.35	4.43	0.50–38.99
Hospital admission (≤1, ≥2 days)	0.78	0.37–1.54	2.35*	1.30–4.22
Congenital malformations (No,Yes)	0.90	0.75–1.07	2.83*	1.07–7.47
Newborn complications (No,Yes)	1.07	0.97–1.19	1.45	0.80–2.60

[†]*pUCI* Postnatal umbilical coiling index, [‡]*PROM* Premature rupture of membrane, [§]*NICU* Neonatal intensive care unit

Statistical analysis: Logistic regression model; pUCI was continuous variable; data are expressed as odds ratio and 95% CI (Confidence interval)

*A *p* value of .05 was considered significant

GDM is reported as an important risk factor for abnormal coiling [5, 24], which has an injurious effect on microscopic, ultrastructural and immunohistochemical aspects of umbilical vessels and Wharton's jelly [8]. Furthermore, the adverse fetal outcomes associated with GDM may have a vascular etiology [8], as the number of coiling or the pathologic vasculature changes. Coiling index is probably one of the most frequently reported umbilical cord related parameters in high risk pregnancies [25].

In the present study, significant difference was found in the rate of spontaneous preterm delivery in GDM in comparison to normal pregnancy, in the other hand, no significant difference was found between the mean of gestational age of two groups. GDM was reported as a risk factor for preterm delivery [26]. The association of pUCI increment with spontaneous preterm delivery in group adjustment was consistent with the findings of de Laat et al., they showed that hypercoiling was an adaptive response to fetal hemodynamic changes [22]. This finding was in contrast with the other studies that the correlation was found between hypocoiling and preterm delivery [1, 24].

Hypercoiling may induce occlusion and torsion of the umbilical vein in cases that suffer of cord entanglement, which lead to compress the fetoplacental blood flow and fetal hypoxia [2], this phenomenon may help us to attribute the etiology of the preterm delivery and meconium staining to this pattern which reserves the fetus regarding to hypoxia. Also another mechanism exists, the fetal blood flows through the umbilical vein, pumped by slight but definitive decreases and increases in venous pressure, caused by adjacent arterial pressure pulses. The arterial coils around the vein along the length provide multiple variations of pressure in an additive fashion, so if the number of coils increases, the effect is larger. In this abnormality, the effect of the arterial pressure pulses may be opposed by increased turbulence in the vessels and compression of the vein [7]. These mechanisms may strengthen and exaggerated in GDM parturients because of the reduction of the Wharton's jelly content, decrement of mucopolysaccharide synthesis and the collagen molecules changes [8].

The correlations between abnormal UCI and the adverse pregnancy outcomes based on de Laat et al. (2006), were as follows: hypocoiled had significant correlation with spontaneous preterm delivery and low apgar score, but no significant correlation was detected between hypercoiled and the mentioned outcomes, in which the population study was the combination of normal and complicated pregnancies and the study was performed on the unclamped cords [1]. On the other hand, in another study, de Laat et al. (2007), reported significant correlations between hypercoiling and preterm delivery, PROM, and LGA. However, hypocoiling was not related to these outcomes [22]. Although, the sample size was bigger than our study, the results were affected by serious selection bias that composed of placentas from cases with adverse pregnancy outcomes. Meanwhile, they reported the outcomes for the complicated parturients irrespective of the presence of co-morbidities.

In Ezimokhai's study a significant association was detected between hypercoiling and meconium staining and emergency cesarean, in which the population study was composed of all parturients [5], which was consistent with Chitra et al. [24]. In Ezimokhai's another study, which was specifically composed of two groups of GDM and non-GDM parturients, similar results were achieved, without multiple logistic regression analysis, they compare the normocoiling with both abnormal patterns [10].

In the present study, hypocoiling was not associated with adverse events, similar to Ezimokhai's study [10]. There were no significant linear relationship between pUCI and the other intrapartum and neonatal outcomes, which may have another non-linear relationship. However, others reported that hypocoiling is significantly associated with meconium staining [2, 24, 27, 28], NICU admission [27] and low apgar score [24, 28].

It is not clear whether abnormal coiling is actually a cause of pathology, or merely one of the sequelae, or both [21]. Abnormal cord coiling, established in early gestation, is a chronic process that may affect fetal well-being acutely (fetal intolerance to labor and fetal demise) or chronically (growth retardation) [4]. Association between UCI abnormality and adverse pregnancy outcome may be explained by several factors including abnormal flow, umbilical cord/venous stenosis or thrombosis, thrombosis of chorionic plate vessels, infection, strength of chorionic and amniotic membranes, and hemodynamic mechanisms. Furthermore, associated aneuploidy/anomalies with subsequent asphyxia and eventually fetal death are other factors [4, 22]. In the other in vitro study, simple differences in mechanical properties of the cord are not the only reasons for the correlation between coiling abnormalities and adverse perinatal outcomes. It can also be explained by growth response of the cord to metabolic and pharmacological abnormalities as well as intrinsic vascular structural changes. In addition, variations in placental morphology affecting placental blood flow and maternal-fetal gas exchange are the other reasons [10, 11]. Placental blood supply decrement; which may affect the number of coils was an important etiology to all mentioned conditions [5].

In some previous studies, the impact of concomitant co-morbidities was not considered in evaluation of intrapartum and neonatal complications. Several other confounding factors, such as considerably varying reference values, no blinding procedures, small sample size, highly selected and/or lack of appropriate control group, outlier effects, and not performing multivariate regression analyses could explain controversial results among the studies.

Conclusion

GDM is associated with spontaneous preterm delivery, PROM, emergency cesarean delivery, duration of hospital admission,

and congenital malformations. Increase in pUCI could increase the rate of spontaneous preterm delivery in normal pregnancy and pregnancy complicated by GDM, as well as, the rate of LGA and meconium-stained amniotic fluid in GDM.

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Compliance with ethical standards

Conflict of interest The authors (Laily Najafi, Mohammad E. Khamseh, Azadeh Abedini, Maryam Kadivar, Alireza Khajavi, Arash Bordbar, Amir Hussein Noohi, Banafsheh Mashak, Maryam Hashemnejad, Mojtaba Malek) declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethical code This project was accepted by ethical committee of Iran University of Medical Sciences; ethical code: IR.IUMS.REC.1393.24991.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants and their spouses included in the study.

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