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ORIGINAL ARTICLE

Relationship between umbilical artery Doppler indices and adverse pregnancy outcomes in women with insulin-dependent diabetes mellitus

Mucize ERİÇ ÖZDEMİR

Department of Perinatology, University of Health Sciences, Turkey. Zeynep Kamil Maternity and Children's Training and Research Hospital, İstanbul, Turkey

ORCID ID
MEÖ : 0000-0002-2177-0771

ABSTRACT

Objective: It is intended to research the value of umbilical artery (UA) and middle cerebral artery (MCA) Doppler indices in predicting adverse pregnancy outcomes in women with insulin-dependent diabetes mellitus.

Material and Methods: The study was planned at Zeynep Kamil Women and Children's Diseases Training and Research Hospital. Pregnant women were divided into two groups: group 1 consisted of 123 fetuses with normal pregnancy outcomes and group 2 had 74 fetuses with adverse pregnancy outcomes. The value of the UA systole/diastole (S/D) ratio was questioned to predict possible adverse pregnancy outcomes. Differences in Doppler measurements between the groups with $p<0.05$ were considered statistically significant.

Results: UA S/D ratios were established as ultrasonographical parameters in predicting normal pregnancy outcomes at 28th, 32nd, and 36th weeks of gestation, with cutoff values of 2.58, 2.56, and 2.62, respectively. Negative predictive values of these three cutoffs for adverse pregnancy outcomes were 70.21%, 72.53%, and 69.03%, respectively.

Conclusion: UA S/D ratios may be helpful to the clinic as ultrasonographical measurements to predict the normal pregnancy outcomes at 28th, 32nd, and 36th weeks of gestation.

Keywords: Diabetes mellitus, Doppler ultrasonography, middle cerebral artery, pregnancy outcome, umbilical artery.

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Correspondence: Mucize ERİÇ ÖZDEMİR, MD. Türkiye Sağlık Bilimleri Üniversitesi, Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi, Perinatoloji Kliniği, İstanbul, Turkey.
Tel: +90 216 391 06 80 **e-mail:** ozdemir.mucize@gmail.com

INTRODUCTION

The physiopathological process that causes negative fetal outcomes in diabetes mellitus (DM) is thought to be multifactorial. Maternal hyperglycemia is strongly associated with fetal macrosomia and hyperinsulinemia, and it has also been associated with elective cesarean delivery, neonatal hypoglycemia, preterm birth, birth trauma, preeclampsia, need for neonatal intensive care, and hyperbilirubinemia.[1] While the cause of the increase in placental vascular resistance in intrauterine growth retardation is structural, the increase in vascular resistance in DM is functional and is related to hyperglycemia. While there are researchers[2] who state that UA Doppler flow is superior to nonstress test and biophysical profile in predicting placental vascular resistance, there are also researchers[3] who say that DM is not associated with abnormality in Doppler indices. In diabetic pregnancies, fetal hypoxia causes an increase in erythropoietin levels in amniotic fluid and cord blood, which is determined by cordocentesis.[4] The increase in blood viscosity due to polycythemia may be reflected as a decrease in middle cerebral artery (MCA) blood flow velocity.[5]

The purpose of the research is to analyze the existence of the connection between UA and MCA Doppler indices and adverse pregnancy outcomes in pregnant women with insulin-dependent DM and to question the usability of these indices in predicting adverse pregnancy outcomes that may develop.

MATERIAL AND METHODS

The study was carried out at the Perinatology Clinic of the University of Health Sciences, Zeynep Kamil Maternity and Children's Training and Research Hospital between May 2019 and November 2020. The ethics committee decision was taken from the center where the study was performed. Written informed consent was received from all pregnant women who participated in the research. Single pregnant women with DM between the ages of 22 and 38 who applied to the perinatology clinic and used insulin were included in the study. Pregnant women with additional systemic disease and those with fetal structural anomaly and severe growth retardation were excluded from the study. Pregnant women who gave birth below 34 weeks were excluded from the study. The sample size was calculated by the formula for comparison of means between two groups.[6] Leung et al.[5] investigated the relationship between Doppler parameters and pregnancy outcomes in women with gestational DM. The sample size, which allowed a 10% attrition rate for outcome variables, was 138 cases. This study examined 220 participants, considering possible technical problems related to ultrasound imaging and loss of follow-up. Screening and diagnosis for DM were determined according to the World Health Organization Criteria.[7] Mid-trimester fetal ultrasound scan, UA, MCA Doppler measurements, and fetal growth measurements were performed at 24th, 28th, 32nd, and 36th weeks of gestation as recommended by the International Society of Ultrasound in Obstetrics and Gynecology.[8,9] Diet and lifestyle changes, glycemic targets, glucose monitoring, and insulin regimens were determined according to the American Diabetes Association 2019 Criteria.[10] Pregnant women using oral antidiabetic in addition to insulin were excluded from the study. From the 28th gestational week, a daily fetal movement count was recommended to the pregnant woman. From the 34th gestational week, the fetal biophysical profile was done twice a week. The week and type of delivery were determined according to glycemic control and obstetric indications. The cases with fasting blood glucose of 95 and above and 140 and above in the first hour of postprandial blood glucose measurements (before and after each meal, three times a day) calculated using a glucometer were considered as pregnant women with poor glycemic control. Measurements were made by a high-risk pregnancy specialist using a 4–8 MHz probe of Voluson E6 (General Electric Medical Systems, Zipf, Austria). A total of 197 pregnant women, whose measurements were completed and delivered at the center where the study was planned after the 34th week, were included in the study. Maternal and fetal complications were determined in 197 pregnant women. The pregnant women who had normal pregnancy outcomes were classified as group 1 and those with adverse pregnancy outcomes were classified as group 2. The two groups were compared in terms of UA systole/diastole (S/D), UA pulsatility index (PI), MCA peak systolic velocity (PSV), and MCA PI indices at 24th, 28th, 32nd, and 36th weeks of gestation. Doppler indices, which were found to be statistically significantly different between the groups, were determined. Cutoff values that can be used to predict adverse pregnancy outcomes were determined, and the receiver operating characteristic (ROC) curve was drawn.

Statistical Analysis

Number Cruncher Statistical System, 2007 (Kaysville, UT, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) were used to evaluate the study data. The conformity of the quantitative data to the normal distribution was tested with the Kolmogorov–Smirnov, Shapiro–Wilk test, and graphical evaluations. Student's t-test was used for two-group comparisons of normally distributed quantitative data, and the Mann–Whitney U test was used for two-group comparisons of nonnormally-distributed data. Pearson's chi-squared test and Fisher–Freeman–Halton exact test were used to compare qualitative data. Diagnostic screening tests (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) and ROC analysis were used to determine the cutoff for parameters. Significance was evaluated at $p<0.05$ level.

RESULTS

Complications were observed in 74 pregnant women. When these complications were examined, 6.8% (n=5) polycythemia, 4.0% (n=3) small for gestational age, 13.5% (n=10) respiratory distress, 5.5% (n=4) low apgar score, 2.7% (n=2) preeclampsia, 9.4% (n=7) jaun dice, 8.2% (n=6) hypoglycemia, 10.8% (n=8) preterm birth, 2.7% (n=2) intrauterine fetal death, 2.7% (n=2) neurological complications, 1.3% (n=1) placental abruption, 1.3% (n=1) birth trauma, 1.3% (n=1) sepsis, 5.5% (n=4) meconium aspiration, 10.8% (n=8) polyhydram nios, and 13.5% (n=10) macrosomia were detected.

Demographic data of 197 pregnant women, who had normal pregnancy outcomes (group 1) and had adverse pregnancy outcomes (group 2), are shown in Table 1. When the two groups were compared in terms of the gestational week at birth and newborn weight, the gestational week at birth and newborn weight were found to be significantly lower in group 2, as expected ($p<0.01$ and $p<0.01$,

Table 1: Demographic and clinical characteristics of the groups

		Group 1 (n=123) n (%)	Group 2 (n=74) n (%)	p
Age (years)	Min–Max (Median)	22–38 (33)	23–38 (33)	0.513[a]
	Mean±SD	32.76±3.46	33.08±3.10	
BMI (kg/m^2)	Min–Max (Median)	21.4–32.9 (27.4)	21.2–32.7 (26.4)	0.384[a]
	Mean±SD	27.00±2.93	26.48±3.35	
Parity	Min–Max (Median)	0–4 (1)	0–3 (1)	0.392[b]
	Mean±SD	1.55±0.98	1.42±1.05	
Daily dose of insulin (IU)	Min–Max (Median)	10–60 (36)	10–57 (38)	0.276[b]
	Mean±SD	35.29±13.05	37.32±11.66	
Types of DM	Type 1	27 (21.4)	20 (27.0)	0.662[c]
	Type 2	85 (67.5)	46 (62.2)	
	GDM	14 (11.1)	8 (10.8)	
HbA1c	Min–Max (Median)	5.9–8 (6.4)	5.9–7.9 (7)	0.083[b]
	Mean±SD	6.70±0.63	6.90±0.70	
Gestational weeks at birth	Min–Max (Median)	37–39.9 (38.3)	34.4–39.9 (38)	**0.001**[*,a]
	Mean±SD	38.28±0.79	37.83±1.07	
Mode of delivery	Vaginal delivery	89 (70.6)	55 (74.3)	0.343[d]
	Elective cesarean section	9 (7.1)	5 (6.8)	
	Urgent cesaren section	28 (22.2)	12 (16.2)	
	Vacum extraction	0 (0)	1 (1.4)	
	Forceps application	0 (0)	1 (1.4)	
Indication for cesarean section	Previous cesarean delivery	9 (24.3)	5 (29.4)	1.000[d]
	Malpresentation	8 (21.6)	3 (17.6)	
	Fetal distress	11 (29.7)	5 (29.4)	
	Cephalopelvic disproportion	9 (24.3)	4 (23.5)	
Induction of labor	None	109 (86.5)	59 (79.7)	0.403[c]
	Prostaglandin	10 (7.9)	10 (13.5)	
	Oxytocin	7 (5.6)	5 (6.8)	
Birth weight (g)	Min–Max (Median)	2701–4244 (3479.5)	1680–4157 (3182)	**0.001**[*,a]
	Mean±SD	3441.54±426.06	3191.39±619.93	
	<4000	112 (88.9)	63 (85.1)	0.438[c]
	>4000	14 (11.1)	11 (14.9)	
Gender of baby	Female	65 (51.6)	40 (54.1)	0.736[c]
	Male	61 (48.4)	34 (45.9)	

a: Student's t-test; b: Mann–Whitney U test; c: Pearson's chi-squared test; d: Fisher–Freeman–Halton exact test; *: p<0.01; DM: Diabetes mellitus; GDM: Gestational diabetes mellitus; HbA1c: Hemoglobin A1c; IU: International unit; Min: Minimum; Max: Maximum; n: Number; SD: Standard deviation; BMI: Body mass index; Group 1 represents pregnant women who had normal pregnancy outcomes and group 2 represents pregnant women who had adverse pregnancy outcomes.

respectively) (Table 1). When UA S/D measurements were compared between the two groups at 24 weeks of gestation, no statistically significant difference was found (p=0.52). UA S/D measurements at the 28th, 32nd, and 36th weeks were found to be significantly higher in group 2 compared with group 1 (p=0.029, p=0.001, and p=0.003, respectively) (Table 2). While MCA PI measurements at week 24 were found to be significantly higher in group 2 than in group 1 (p=0.033), 28th, 32nd, and 36th weeks MCA PI measurements did not differ statistically between the two groups (p>0.05). Cutoff values were determined using diagnostic screening tests and ROC analysis for Doppler indices (UA S/D of 28th, 32nd, and 36th weeks), which were found to be statistically and clinically significant in terms of predicting adverse

Table 2: UA PI, UA S/D, MCA PSV, and MCA PI measurements at 24th, 28th, 32nd, and 36th weeks of the groups

		Group 1 (n=123) Mean±SD	Group 2 (n=74) Mean±SD	p
UA PI	24th week	1.28±0.23	1.30±0.24	0.520
	28th week	1.20±0.24	1.18±0.26	0.672
	32nd week	1.10±0.25	1.16±0.25	0.099
	36th week	0.99±0.24	1.04±0.32	0.237
UA S/D	24th week	2.58±0.18	2.59±0.23	0.725
	28th week	2.57±0.18	2.66±0.31	**0.029***
	32nd week	2.55±0.17	2.71±0.41	**0.001****
	36th week	2.57±0.16	2.73±0.45	**0.003****
MCA PSV	24th week	30.66±5.48	30.43±5.75	0.772
	28th week	39.44±7.07	40.12±7.63	0.522
	32nd week	49.47±8.96	48.93±10.60	0.716
	36th week	55.82±10.79	53.56±13.48	0.222
MCA PI	24th week	1.90±0.42	2.03±0.41	**0.033***
	28th week	2.30±0.46	2.26±0.42	0.561
	32nd week	2.32±0.45	2.31±0.43	0.853
	36th week	1.98±0.38	2.05±0.41	0.267

Student's t test; *: p<0.05; **: p<0.01; n: Number; PI: Pulsatility index; MCA: Middle cerebral artery; PSV: Peak systolic velocity; S/D: Systole/diastole; SD: Standard deviation: UA: Umbilical artery; Group 1 represents pregnant women who had normal pregnancy outcomes and group 2 represents pregnant women who had adverse pregnancy outcomes.

pregnancy outcomes (Table 3). According to the incidence of adverse pregnancy outcomes, the cutoff value of UA S/D measurements at the 28th week was found to be 2.58 and above. For the 2.58 cutoff value of the 28th week UA S/D measurements, sensitivity was 62.16%, specificity was 52.38%, PPV was 43.40%, NPV was 70.21%, and accuracy was 56%. The area under the ROC curve obtained was 56.6% and the standard error was 4.2% (Table 3). A statistically significant correlation was found between the occurrence of adverse pregnancy outcomes and the 2.58 cutoff value of UA S/D measurements at 28 weeks (p=0.047). In cases with UA S/D measurements of 2.58 and above at 28 weeks, the risk of adverse pregnancy outcomes was 1.807 times higher. The odds ratio for UA S/D measurements at week 28 was 1.807 (95% CI: 1.006–3.246) (Table 4). The cutoff value for UA S/D measurements at 32nd weeks was found to be 2.56 and above, depending on the incidence of adverse pregnancy outcomes. For the 2.56 cutoff value of the 32nd week UA S/D measurements, sensitivity was 66.22%, specificity was 52.38%, PPV was 44.95%, NPV was 72.53%, and accuracy was 57.50%. The standard error of the area under the ROC curve obtained was 62.1% and 4.2% (Table 3). A statistically significant correlation was found between the occurrence of adverse pregnancy outcomes and the 2.56 cutoff value of UA S/D measurements at 32 weeks (p=0.011). In cases with UA S/D measurements of 2.56 and above at 32 weeks, the risk of adverse pregnancy outcomes was 2.156 times higher. The odds ratio for UA S/D measurements at week 32 was 2.156 (95% CI: 1.189–3.910) (Table 4). The cutoff value for UA S/D measurements at 36 weeks was found to be 2.62 and above, depending on the incidence of adverse pregnancy outcomes. For the 2.62 cutoff value of the 36th week UA S/D measurements, sensitivity was 52.70%, specificity was 61.90%, PPV was 44.83%, NPV was 69.03%, and accuracy was 58.50%. The standard error of the area under the ROC curve obtained was 58.3% and 4.4% (Table 3). A statistically significant correlation was found between the occurrence of adverse pregnancy outcomes and the cutoff value of 2.62 for UA S/D measurements at 36 weeks (p=0.044). The risk of adverse pregnancy outcomes was 1.811 times higher in cases with UA S/D measurements of 2.62 and above at 36 weeks. The odds ratio for UA S/D measurements at week 36 was 1.811 (95% CI: 1.013–3.237) (Table 4). The ROC curve of UA S/D measurements at 28th, 32nd, and 36th weeks of gestation according to the incidence of adverse pregnancy outcomes is shown in Figure 1.

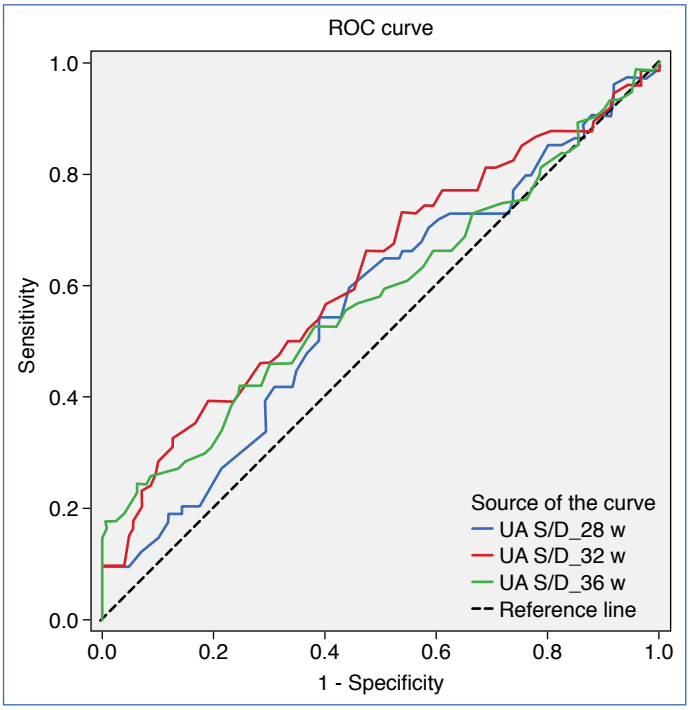

Figure 1: Receiver operating characteristic (ROC) curves for UA systole/diastole (S/D) measurements at 28th, 32nd, and 36th weeks to predict adverse pregnancy outcomes.

Receiver operating characteristic curves for the UA S/D Doppler parameters to predict adverse pregnancy outcomes. Blue line indicates week 28. Red line indicates week 32. Green line indicates week 36. Black dotted line indicates the reference line.

DISCUSSION

Although the relationship between impaired venous/arterial Doppler indices and poor pregnancy outcomes in intrauterine growth retardation and fetal anemia was well defined,[11,12] the same relationship has not been clarified in pregnant women with DM.[2,3,13–19] Pregnant women with DM who are treated and maintain adequate glycemic control show a significant decrease in adverse perinatal outcomes. In addition to close glycemic control, the availability of arterial Dop-

Table 3: Diagnostic screening tests and ROC curve results for UA S/D measurements at 28th, 32nd, and 36th weeks according to adverse pregnancy outcomes

UA S/D	Cutoff	Sensitivity	Specificity	PPV	NPV	AuC	95% CI	p
28th week	≥2.58	62.16	52.38	43.40	70.21	**0.566**	0.483–0.649	**0.049***
32nd week	≥2.56	66.22	52.38	44.95	72.53	**0.621**	0.538–0.703	**0.004****
36th week	≥2.62	52.70	61.90	44.83	69.03	**0.583**	0.497–0.669	**0.049***

*: p<0.05; **: p<0.01; AuC: Area under the curve; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value; ROC: Receiver operating characteristic; S/D: sistole/diastole; UA: Umbilical artery.

Table 4: Relationship between adverse pregnancy outcomes and UA S/D measurements at 28th, 32nd, and 36th weeks

		Group 1		Group 2		p
		n	%	n	%	
28th UA S/D	<2.58	66	52.4	28	37.8	0.047*,a
	≥2.58	60	47.6	46	62.2	
32nd UA S/D	<2.56	66	52.4	25	33.8	0.011*,a
	≥2.56	60	47.6	49	66.2	
36th UA S/D	<2.62	78	61.9	35	47.3	0.044*,a
	≥2.62	48	38.1	39	52.7	

a: Pearson's chi-squared test; *: p<0.05; n: Number; S/D: Systole/diastole; UA: Umbilical artery; Group 1 represents pregnant women who had normal pregnancy outcomes and group 2 represents pregnant women who had adverse pregnancy outcomes.

pler indices to predict maternal, fetal, and neonatal complications may help the clinician in the management of these patients. The purpose of the research is to examine the existence of the connection between UA and MCA Doppler indices and adverse pregnancy outcomes in pregnant women with insulin-dependent DM and to question the usability of these indices in predicting adverse pregnancy outcomes that may develop. Leung et al.[5] investigated the relationship between UA PI, MCA PI, and MCA PSV indices and pregnancy complications in pregnant women with gestational DM and did not find these indices useful in predicting poor pregnancy outcomes. Measurement of Doppler indices with an interval of 4 weeks was planned, but only 4 measurements could be made on 11 pregnant women, and 36 pregnant women were evaluated with a single measurement. Only 7.9% of the pregnant women had DM using insulin and 84.7% had only impaired glucose tolerance. The complication rate was found to be 27.5%. Leung suggested that these indices be studied in poorly controlled pregnant women with pregestational DM. In the current study, the complication rate was found to be 37%, and this high rate may be due to high mean blood sugar level (Type 1 DM 27%, Type 2 DM 62.2%, GDMA2 8%) in pregnant women who participated in the study. When the two groups were compared in terms of adverse pregnancy outcomes, no differences were found in the type of DM, total daily insulin dose, and HbA1c levels. This result proves that other factors such as circulatory factors other than target blood glucose levels cause poor pregnancy outcomes in diabetic pregnant women. In addition, since maternal glycemic control may affect Doppler results as a confounding factor,[3] the absence of difference in HbA1c levels between the two groups compared may partially facilitate the interpretation of the results. In the current study, UA S/D measurements in group 2 were found to be higher than group 1 at 28th, 32nd, and 36th weeks, and this difference was statistically significant (p=0.029, p=0.001, and p=0.003, respectively). Abnormalities in the structure of placental blood vessels, such as the increase in the surface area of tertiary villi and the increase in the diffusion distance between maternal–fetal blood flow, may cause Doppler flow changes in the umbilical arteries in pregnant women with DM.[20] As the study included only pregnant women using insulin, the hemodynamic and metabolic effects of DM on the UA may have been strongly reflected. In the study of Dantas et al.,[21] MCA PI measurements in pregnant women with DM were not different from those without DM. Although MCA PSV was found to be low in pregnant women with diabetes, this result was not associated with fetal macrosomia and inadequate glucose control. In the current study, MCA PI was found to be statistically significantly higher in group 2 compared to group 1 at week 24, but this elevation was not found to be clinically significant. There was no difference between the two groups in terms of MCA PSV measurements, which may be related to the detection of polycythemia in only 3 newborns in the study. When Doppler indices were evaluated in terms of newborn weight, the UA PI value at 28 weeks was found to be significantly higher in babies born over 4000 g (n=25, 13.6%) compared with babies born under 4000 g (p<0.001). In the study of Maruotti et al.,[22] UA PI value in pregnants with Type 1 DM was found to be significantly lower in macrosomal fetuses than in cases without fetal growth. According to the study of Quintero-Prado et al.,[23] UA PI value can predict birth weight in women with gestational DM. In the current study, the relationship between UA PI value and macrosomia contradicts the literature, and this may depend on the population of the study, the gestational week where the measurement was made, and the type of DM. In this study, regression analysis was performed by determining the sensitivity, specificity, PPV, and NPV, and ROC curves were created for the S/D ratio of UA at 28th, 32nd, and 36th weeks of gestation. If UA S/D measurement <2.58 at 28 weeks, <2.56 at 32 weeks, and <2.62 at 36 weeks then this may help us to predict that pregnancy complications will not develop with a probability of 70.2%, 72.5%, and 69.0%, respectively.

Study Limitation

The research was conducted by an expert with a small number of pregnant women in the same population. Therefore, many studies should be done to support the findings.

CONCLUSION

It should not be forgotten that metabolic control is the most important marker in the prediction of maternal–fetal–neonatal complications in pregnant women with DM. Although increased Doppler indices in diabetic pregnancies are associated with adverse pregnancy outcomes, the Doppler indices may be increased in fetuses with normal outcomes due to the accompanying microvascular disease. Therefore, care should be taken when interpreting Doppler indices in the evaluation of fetal well-being in diabetic pregnant women.[24]

Statement

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Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 18.04.2018, number: 69).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflict of interest to declare.

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