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Prediction of preeclampsia using a combination of serum micro RNA-210 and uterine artery Doppler ultrasound

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Abstract

The objective was to determine whether a combination of serum micro RNA-210 level and uterine artery Doppler can predict preeclampsia in pregnant women at 16–24 weeks gestation. A prospective observational study conducted in singleton pregnant women at 16–24 weeks of gestation who had prenatal care at the King Chulalongkorn Memorial Hospital, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand between 2017 and 2018. Uterine artery Doppler ultrasound and blood testing for serum micro RNA-210 were performed. Pregnancy outcomes were recorded. Optimal cut-off for uterine artery pulsatility index (PI) and serum micro RNA-210 were obtained to calculate the predictive values for preeclampsia. Data from 443 participants were analyzed. Twenty-two cases developed preeclampsia (5.0%) and seven of these preeclamptic cases had early-onset preeclampsia (1.6%). Pregnant women with preeclampsia had higher mean PI of the uterine artery (1.34 ± 0.52 vs 0.98 ± 0.28, $p = 0.004$), higher detection rates of diastolic notching (45.5% vs 11.2%, $p < 0.001$), and lower median serum micro RNA-210 level (22.86 vs 795.78, $p < 0.001$) than pregnant women without preeclampsia. Using abnormal serum micro RNA-210 level, abnormal mean PI or uterine artery diastolic notches to predict for preeclampsia, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 95.5%, 54.9%, 10.0%, and 99.6%, respectively. For early-onset preeclampsia prediction, the sensitivity, specificity, PPV, and NPV were 100.0%, 53.2%, 3.3%, and 100.0%, respectively. This study demonstrated that a combination of serum micro RNA-210 and uterine artery Doppler is effective in predicting preeclampsia in the second trimester.

Keywords

Preeclampsia, predictive value, uterine artery Doppler, serum micro-RNA 210

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Introduction

Preeclampsia is a common pregnancy disorder. It contributes to maternal and neonatal morbidity and mortality. It is one of the three most common causes of maternal death in the world. Preeclampsia is defined as having a blood pressure of ⩾140/90 mmHg or more on two occasions at least 4 h apart accompanied by proteinuria (⩾300 mg/dL of protein in a 24-h urine collection, or a urine protein-to-creatinine ratio ⩾0.3, or ⩾1 + on urine dipstick) after 20 weeks of gestation.[1] The incidence of preeclampsia is approximately 2%–8% of pregnancies.[2,3] There are many strategies proposed to prevent preeclampsia. The United States preventive services task force recommend that women with any high-risk factors for preeclampsia should receive a low dose of acetylsalicylic acid (ASA) (60–150 mg/day) for preeclampsia prophylaxis administered between 12 and 28 weeks of gestation.[4] Identification of pregnant women at high-risk can improve pregnancy outcomes, either by early and frequent surveillance or the consideration to start ASA in high-risk patients.

Although the exact pathophysiology of preeclampsia is still unknown, several mechanisms of the disease have been proposed including a two-stage model.[5] In the first stage, the process of trophoblast invasion to spiral arteries is impaired resulting in a poorly perfused placenta. Increased vascular resistance of the uterine artery indicates failed remodeling of the vessels of the intervillous space.[3,5,6] A systematic reviews showed that an increase of uterine artery pulsatility index (PI) alone and/or combined with the presence of a uterine artery notching are better predictors of preeclampsia in the second trimester than in the first trimester.[7] Angiogenic imbalance is another hypothesis. This imbalance can be evaluated by the measurement of angiogenic factors. Increased maternal soluble fms-like tyrosine kinase 1 (sFlt-1) levels inactivate and decrease circulating placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) concentrations and have shown an important factor in preeclampsia pathogenesis. This causes hypertension and proteinuria.[8]

In the second stage, maternal constitutional factors (genetic, behavioral, or environmental) are considered important because they can cause clinical manifestations of preeclampsia.[5] Genetic factors are thought to have an important role in placental development.[9] Because placenta is in direct contact with maternal circulation, cellular products (deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and proteins from the placenta can be detected in maternal serum which can be used to predict many diseases.[9] Micro RNAs are small (approximately 22 nucleotides) noncoding RNAs that regulate gene expression at the post-transcription level.[10] They have emerged as key regulators of gene expression stability implicated in cell proliferation, apoptosis, and development.[11] They also contribute to the conception and maintenance of pregnancy by regulating key processes such as inflammation, immune tolerance, angiogenesis, and apoptosis.[12] One micro RNA can regulate the expression of multiple genes and one gene can be targeted by more than one micro RNA.[10] Up to 60% of the human genes are targeted by at least one micro RNA.[13]

Micro RNA-210 is a common hypoxia-induced micro RNA involved in many biological processes, including angiogenesis, cell differentiation, cell cycle regulation, proliferation and growth, inflammation, DNA damage repair, and

mitochondrial metabolism.[14] Because these processes have been shown to be abnormally regulated in preeclampsia, previous studies have evaluated micro RNA-210 expression in preeclampsia. Some studies found increased micro RNA-210 expression in preeclamptic placentas,[15,16] and serum.[14,17] Some studies found decreased micro RNA-210 expression in mild preeclamptic placentas.[18,19]

There are many studies that are trying to find a marker that can predict preeclampsia. However, there is no single marker that can effectively predict preeclampsia. Studies that have evaluated a combination of markers demonstrated that it was more effective in predicting preeclampsia than a single marker.[20,21] Thus, the objective of this study was to determine the predictive value of a combination of serum micro RNA-210 level and uterine artery Doppler to predict preeclampsia in women at 16–24 weeks' gestation and to identify the predictive value for other pregnancy complications by using this combined test.

Methods

This prospective observational study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand from December 2017 to October 2018. The study was approved by the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University. Written informed consent was obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations of the Institutional Review Board.

Singleton pregnant women, age at least 18 years with a gestational age of 16–24 weeks were invited to participate in the study. Pregnant women were recruited consecutively. Gestational age was calculated from the last menstrual period and confirmed by first-trimester ultrasound. Women with underlying cancer that may affect serum micro RNA-210 level, had a history of ASA use, had preexisting hypertension, and had fetal abnormalities (structural or chromosomal) were excluded from the study. Sample size calculation was based on a previous study's sensitivity to predict preeclampsia (75%)[14] with 20% allowable error ($\alpha = 0.05$, $\beta = 0.2$). This indicated that the study needed 18 cases of preeclampsia. The incidence of preeclampsia at our institute was 4.2%. After we adjusted the calculation using our institute's incidence of preeclampsia and a loss to follow-up rate of 20%, a minimum of 451 women were required for this study. The primary outcome was the diagnosis of preeclampsia. Preeclampsia was defined as having a blood pressure of $\geq$140/90 mmHg or more on two occasions at least 4 h apart accompanied by proteinuria ($\geq$300 mg/dL of protein in a 24-h urine collection, or a urine protein-to-creatinine ratio $\geq$0.3, or $\geq$1 + on urine dipstick) after 20 weeks of gestation.[1] Early-onset preeclampsia was defined as preeclampsia that occurred before gestational age 34 weeks.[22] Secondary outcomes included preterm delivery, and fetal growth restriction (FGR). The maternal demographic data, uterine artery Doppler PI, serum micro RNA-210, and maternal and neonatal outcomes were recorded.

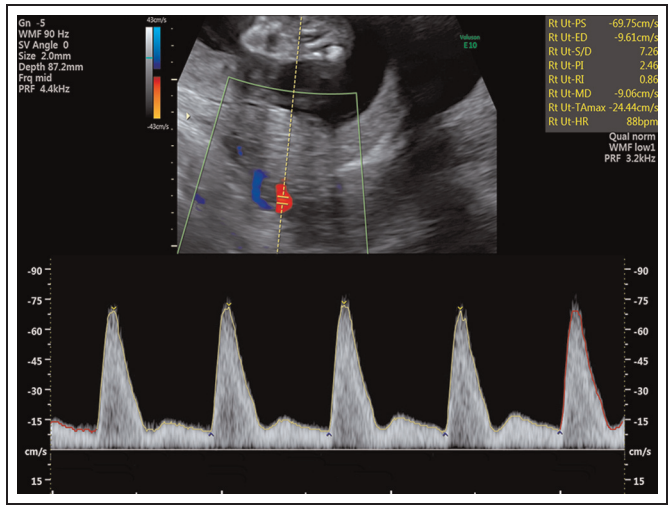

Figure 1. Sonographic images of the uterine artery Doppler waveform with notching.

Uterine artery Doppler evaluation

Uterine artery flow velocity waveforms were obtained by using ultrasonographic machines (GE Voluson E10, GE Medical Systems, Milwaukee, WI) with a convex abdominal probe AB 2–7MHz by a single operator. Each participant was examined once in the semi-recumbent position after 5 min of bedrest. The uterine artery was visualized by placing the probe longitudinally at the lower lateral quadrant of the abdomen, angled medially. Flow velocity waveforms were obtained from each uterine artery where it crossed the external iliac artery with an angle of insonation $<30°$ as performed in previous studies.[21,23] The size of the Doppler sample gate was 2 mm. The machine's mechanical index and thermal index during the Doppler scans were 0.8 ± 0.06 and 0.25 ± 0.14. At least three waveforms from each side were recorded. Mean PI was calculated, and the presence or absence of an early diastolic notch was noted (Figure 1). A uterine notch was defined as a definite upward change in velocity after the deceleration slope of the primary wave.[21,23] In order to eliminate bias, the investigator who performed the uterine artery Doppler ultrasound was not the same ones who made a diagnosis of preeclampsia in those who had it.

Sample collection and serum micro RNA-210 detection

After Doppler examination, venipuncture was performed, and blood was collected into non-heparinized blood tubes at the same period (08.00–09.00 am). Blood samples were then centrifuged at 2500 rounds per minute for 10 min. Subsequently, serum was transferred to a new collection tube and stored at $-80°C$ until assayed. Total RNA was extracted from 200 μL serum using the Geneaid miRNA isolation

kit (RMI050, New Taipei City, Taiwan, R.O.C.) following the manufacturer's instructions. Micro RNA-210 and RNA U6-specific cDNA sequences were synthesized from total RNA using gene-specific primer and reverse transcription kit. Reverse transcription (RT) reactions contained 12.5 μL of total RNA, 5 μL of RT primer, 4 μL of 5 × RT buffer, 2 μL of dNTP (10 mmol/L), 1 μL of RevertAid, and 0.5 μL of RNase inhibitor. The 25 μL reaction mixture was incubated at 42°C for 60 min, and 70°C for 10 min, then held at 4°C. Expression of micro RNA-210 was assessed by the SYBR Green-based real-time polymerized chain reaction (PCR) method. The thermocycling program consisted of 40 cycles of 95°C for 15 s, 60°C for 15 s, and 72°C for 32 s. A small nuclear RNA U6 was used as an internal control. All PCRs were performed in duplicates. Relative micro RNAs expression values were calculated by the $2^{-\Delta}$CT method.

Statistical analysis

Data were analyzed with the SPSS software package version 22.0 for Windows (SPSS, Chicago, USA) and are expressed as mean, standard deviation, median, interquartile range, sensitivity, specificity, PPV, NPV, and relative risk (RR) with a 95% confidence interval (CI). The optimal cut-off values for uterine artery PI and micro RNA-210 were calculated using the receiver operator characteristic curve. A chi-square test and Fisher's exact test were used for categorical variables. An independent *t*-test was used for continuous variables. The Mann–Whitney *U* test was used for nonparametric variables. RR was calculated. A p-value < 0.05 was considered statistically significant.

Results

A total of 451 pregnant women were enrolled into this study, and eight participants were excluded from the study (four cases had thalassemia major, two cases had abnormal structural fetuses, and two cases had abnormal chromosomal fetus). Data from 443 participants were analyzed. Twenty-two cases developed preeclampsia (5.0%) and seven of these preeclamptic cases had early-onset preeclampsia (1.6%). Clinical characteristics between healthy pregnant women and pregnant women with preeclampsia are shown in Table 1. Mean arterial pressure was higher in pregnant women with preeclampsia. Pregnant women with preeclampsia had higher rates of preterm delivery, intrauterine growth restriction, and low birthweights than normal pregnant women.

Pregnant women with preeclampsia and early-onset preeclampsia had higher mean PIs of the uterine artery and higher detection rates of diastolic notching than normal pregnant women (Table 2). Based on the receiver operator characteristic curve (AUC = 0.692, 95% CI: 0.565–0.820, $p = 0.002$), the optimal cut-off value for mean uterine artery Doppler PI was 1.025. When uterine artery Doppler PI above 1.025 or diastolic notches was used, the prediction of overall preeclampsia (Table 3) were as follows: the sensitivity was 68.2%, the specificity was 64.5%, the

Table 1. Basic characteristics data, maternal, and neonatal outcomes.

	Control ($n = 421$)	Preeclampsia ($n = 22$)	p Value
Age (years)	35.2 ± 4.7	35.6 ± 3.3	0.722
Primigravida	148 (35.2)	7 (31.8)	0.749
Parity			0.163
0	199 (47.0)	7 (31.8)	
⩾1	223 (53.0)	15 (68.2)	
Pre-pregnancy BMI (kg/m^2)	23.1 ± 4.1	24.7 ± 4.7	0.067
Obesity (BMI ⩾ 30 kg/m^2)	29 (6.9)	3 (13.6)	0.233
Mean arterial pressure (mmHg)	83.8 ± 8.7	87.9 ± 8.7	0.033
GA at measurement (weeks)	18.7 ± 1.7	18.5 ± 1.6	0.472
GA at delivery (weeks)	38.4 ± 1.7	37.7 ± 2.5	0.206
Delivery at GA < 37 weeks	39 (9.3)	6 (27.3)	0.006
Delivery at GA < 34 weeks	6 (1.4)	2 (9.1)	0.008
Mode of delivery			0.118
Vaginal delivery	156 (37.1)	3 (13.6)	
Cesarean delivery	256 (60.8)	19 (86.4)	
Birthweight (grams)	3065.2 ± 434.9	2679.9 ± 684.7	0.016
FGR	3 (0.7)	4 (18.2)	<0.001
Apgar score			
<7 at 1 min	6 (1.4)	0	1.000
<7 at 5 min	2 (0.5)	0	1.000

Data are presented as mean ± SD or n (%).
BMI: body mass index; FGR: fetal growth restriction; GA: gestational age.

Table 2. Characteristics of the uterine artery Doppler and serum micro RNA-210 level.

	Control ($n = 421$)	Preeclampsia ($n = 22$)	Early-onset preeclampsia ($n = 7$)	p Value
UtA PI	0.98 ± 0.28	1.34 ± 0.52		0.004
			1.63 ± 0.62	0.03
Notching	47 (11.2)	10 (45.5)		<0.001
			4 (57.1)	<0.001
Micro RNA-210	795.78 (112.20, 4865.90)	22.86 (8.04, 1177.85)		<0.001
			8.46 (2.51, 2091.69)	0.017

Data are presented as mean ± SD, median (IQR), or n (%).
RNA: ribonucleic acid; UtA PI: uterine artery pulsatility index.

PPV was 9.1%, and NPV was 97.5%. As for the prediction of early-onset preeclampsia, the sensitivity, specificity, PPV, and NPV were 71.4%, 63.5%, 3.0%, and 99.3%, respectively (Table 3).

Pregnant women with preeclampsia and early-onset preeclampsia had significantly lower median serum micro RNA-210 than pregnant women without preeclampsia (Table 2). Based on the receiver operator characteristic curve

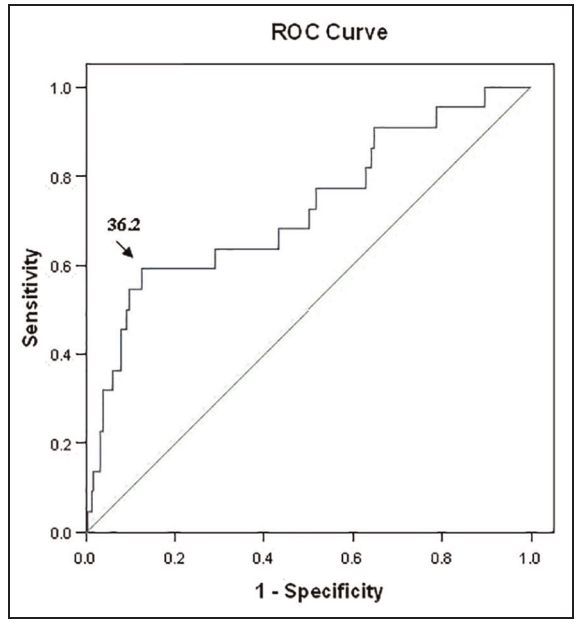

Figure 2. Receiver operator characteristic curve for the relationship between serum micro RNA-210 level and the diagnosis of preeclampsia (AUC = 0.725, 95% CI: 0.603–0.848, $p < 0.001$).

(AUC = 0.725, 95% CI: 0.603–0.848, $p < 0.001$), the optimal cut-off value for serum micro RNA-210 was 36.2 (Figure 2). When the serum micro RNA-210 cut-off value below 36.2 was used to predict the overall preeclampsia, the sensitivity, specificity, PPV, and NPV were 59.1%, 87.4%, 19.7%, and 97.6%, respectively. As for the prediction of early-onset preeclampsia, the sensitivity, specificity, PPV, and NPV were 57.1%, 85.8%, 6.1%, and 99.2%, respectively (Table 3).

Using uterine artery PIs above 1.025 or diastolic notches or serum micro RNA-210 below 36.2 for preeclampsia prediction, the sensitivity, specificity, PPV, and NPV were 95.5%, 54.9%, 10.0%, and 99.6%, respectively (Table 3). For early-onset preeclampsia prediction, the sensitivity, specificity, PPV, and NPV were 100.0%, 53.2%, 3.3%, and 100.0%, respectively (Table 3).

Participants with an abnormal uterine artery PI (PI above 1.025 or diastolic notches) combined with abnormal serum micro RNA-210 (below 36.2) were at a higher risk for preterm delivery and fetal growth restriction (FGR).

Discussion

This study showed that a combination of serum micro RNA-210 and uterine artery Doppler is effective in predicting preeclampsia in the second trimester.

Table 3. The predictive value of uterine artery Doppler and serum micro RNA-210 level for preeclampsia.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Positive LR	Negative LR
Overall preeclampsia						
Mean PI>1.025 or notching	68.2	64.5	9.1	97.5	1.9	0.5
Micro RNA-210<36.2	59.1	87.4	19.7	97.6	4.7	0.5
Mean PI>1.025 or notching or Micro RNA-210<36.2	95.5	54.9	10.0	99.6	2.1	0.1
Notching or micro RNA-210<36.2	86.4	76.7	16.2	99.1	3.7	0.2
Early-onset preeclampsia						
Mean PI>1.025 or notching	71.4	63.5	3.0	99.3	2.0	0.4
Micro RNA-210<36.2	57.1	85.8	6.1	99.2	4.0	0.5
Mean PI>1.025 or notching or micro RNA-210<36.2	100.0	53.2	3.3	100.0	2.1	0.0
Notching or micro RNA-210<36.2	85.7	74.5	5.1	99.7	3.4	0.2

PI: pulsatility index; RNA: ribonucleic acid.

Micro RNA-210 has a pro-survival, cytoprotective, and pro-angiogenic role.[24] It has a very important role in gene regulation and may be used as a marker for stage 2. Thus, when uterine artery Doppler is used with serum micro RNA-210 to predict preeclampsia, both of these tests may complement each other, resulting in increased efficacy. This finding was consistent with previous studies that showed a combination use of the uterine artery Doppler and biochemical factors had a better efficacy in predicting preeclampsia.[25,26]

Mean arterial pressure was higher in pregnant women who later developed preeclampsia in this study. Previous study found that combined screening by maternal factors, uterine artery pulsatility index, mean arterial pressure, and placental growth factor predicted 75% (95% CI: 70%–80%) of preterm-preeclampsia and 47% (95% CI: 44%–51%) of term-preeclampsia, at a false-positive rate of 10%.[27]

Using uterine artery Doppler (mean PI > 1.025 or notching) or serum micro RNA-210 levels at 16–24 weeks of gestation to predict preeclampsia had a higher sensitivity but lower specificity when compared with previous studies that examined the combination use of uterine artery Doppler with other biochemical factors.[25] When abnormal uterine artery Doppler or serum micro RNA-210 was used to predict early-onset preeclampsia, there was a higher sensitivity than to predict overall preeclampsia. This result confirmed a combination of uterine artery Doppler and

biochemical markers could predict early-onset preeclampsia better than overall preeclampsia as demonstrated from previous studies.[21,26,28–30]

The combination use of biochemical marker and uterine artery Doppler in this study had sensitivity similar to previous studies that use of biochemical marker and uterine artery Doppler in prediction of preeclampsia and FGR.[31–33] Sonek et al.[31] performed first-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume. They found that the detection rate of early-onset preeclampsia for either 5% or 10% false-positive rate was 85%. Spencer et al.[32] performed a study of first-trimester maternal serum placental protein-13 (PP-13), pregnancy-associated plasma protein-A (PAPP-A), and second-trimester uterine artery Doppler pulsatility index as markers of preeclampsia. They found that combining PP-13 and PI had sensitivity of 74% for prediction of preeclampsia and 79% for early-onset preeclampsia. PAPP-A with PI had a sensitivity of 76% for prediction of preeclampsia. But, combining PAPP-A with PP-13 and PI did not add significantly to the sensitivity. He et al. performed first-trimester screening for FGR using Doppler color flow analysis of the uterine artery and serum PAPP-A levels in unselected pregnancies. They found that the sensitivity and specificity of combination of uterine artery Doppler and PAPP-A for prediction of FGR were 81.6% and 75.8%, respectively.[33] The result of this study was better than Goetzinger et al.'s[34] study. They performed a study of first-trimester uterine artery Doppler, a-disintegrin and metalloprotease 12, PAPP-A, and maternal characteristics in the prediction of preeclampsia. They found that combining these first-trimester parameters identified 50% of patients who developed preeclampsia. They concluded that combining these first-trimester parameters did not improve the predictive efficiency of the models.[34]

The serum micro RNA-210 in pregnant women with preeclampsia in this study was significantly lower than normal pregnant women. The function of micro RNA-210 is complicated and may be dependent upon the time and the environment.[24] Micro RNA-210 has a critical role in supporting cell survival, VEGF-driven endothelial cell migration, and the ability of endothelial cells to form capillary-like structures.[24,35,36] In preeclampsia women, underexpression of micro RNA-210 can lead to a defect in the placental vascular remodeling process. This finding is consistent with a decrease in serum micro RNA-210 level in other ischemic diseases such as stroke.[37]

This study was the first prospective study that used a combination of serum micro RNA-210 with uterine artery Doppler to predict preeclampsia. The cost for a single RNA-210 determination was 40 USD. Our unique study used a combination test to predict preeclampsia during the second trimester screening test using ultrasonographic examination to detect fetal anomaly. This was convenient for the participants because the two screenings tests were performed in one visit. It should be noted that if these combination tests were performed in the first trimester, ASA may have been started earlier to prevent preeclampsia. Additional prospective study using this combination test at an earlier gestational age should be conducted to evaluate the usefulness of this combination test. A notable limitation of this study was the small number of participants with early-onset preeclampsia.

Conclusion

A combination of serum micro RNA-210 and uterine artery Doppler at 16–24 weeks of gestation was effective in predicting preeclampsia. This combination test may be useful as a second trimester screening test for preeclampsia.

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Declaration of conflicting interests

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Ethics approval

Ethical approval to report this research was obtained from the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University (IRB no. 561/60).

Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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