





# Effects of Methamphetamine Use in Pregnant Women: Neonatal Affect and Role of Inflammatory Markers

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## ABSTRACT

**Objective:** To investigate the relationship between inflammatory markers in methamphetamine (MA) abuse during pregnancy and develop a screening tool.

**Material and Methods:** This was a retrospective cohort study of pregnant women who gave birth at Nakhon Phanom Hospital (NPH), Thailand, between January 2022 and December 2023. Subjects were parturients who delivered at NPH during the study period and obtained MA detection by spot urine sample test at first antenatal care and delivery. Participants with positive and negative urine MA were placed in the study and control group, respectively. Data came from hospital electronic records and were analyzed to create inflammatory markers.

**Results:** There were 87 and 234 subjects in the study and control groups, respectively. The prevalence of MA during pregnancy was 2.4%. The average age and body mass index of participants were 27.5 years old and 27 kg/m<sup>2</sup>, respectively. The study group had a higher risk of preterm labor than the control group (OR 5.7, p<0.01). Only the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), and systemic immune inflammation index (SII) were significant prognostic factors and generated a predictive model (MA score). Predictive model gave a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios at 57.5%, 83.8%, 56.8%, 84.1%, 3.5, and 0.5, respectively.

**Conclusion:** MA usage during pregnancy affected to preterm delivery. NLR, PLR, MLR, and SII were associated with MA addiction. The MA score was an easy tool to estimate the probability of MA use in pregnancy when MA screening was not routinely performed.

**Keywords:** Methamphetamine; Pregnancy; Inflammatory markers

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Methamphetamine (MA) is a widely abused drug worldwide. In 2020, it was found that 34 million people globally were using this substance<sup>(1)</sup>. In Asia, over 12 million people were reported to use this drug, particularly in East Asia and Southeast Asia<sup>(1)</sup>. In Thailand, MA is among the most commonly used recreational drugs in the country. It ranks the highest in terms of seizures globally<sup>(1,2)</sup>.

In Thailand, there has been an increase in the number of pregnant mothers using amphetamine-type

### What is already known about this topic?

MA usage during pregnancy has significant impacts on both mother and fetus, namely gestational hypertension, preeclampsia, placental abruption, and maternal anemia. MA addiction can compromise the immune response. NLR, PLR, MLR, and SII are inexpensive determinants of inflammation and potentially indicate MA use in pregnant women.

### What does this study add?

MA score conducted from NLR, PLR, MLR, and SII gave sensitivity, specificity, PPV, and NPV at 57.5%, 83.8%, 56.8%, and 84.1%, respectively.

stimulants (ATS), rising from 0.46% to 1.28% during 2008 and 2015<sup>(3)</sup>. One study in Thailand found a noticeable increase in the number of pregnant women who used MA while giving birth<sup>(4)</sup>. Specifically, from 2011 to 2013, the percentage of newborns born to mothers who had used MA in Thailand was 1.13%, 1.15%, and 1.4%, respectively<sup>(4)</sup>.

MA has two enantiomers: d-methamphetamine and l-methamphetamine. D-methamphetamine has stronger stimulant properties, resulting in a higher potential for abuse<sup>(5)</sup>. MA affects the central nervous system and impacts the secretion and metabolism of neurotransmitters such as dopamine, serotonin,

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and norepinephrine. Neurotransmitters can lead to increased energy, feelings of euphoria, and induced psychosis<sup>(2,6)</sup>. The use of MA during pregnancy can have significant impacts on both the mother and fetus. It is associated with complications such as gestational hypertension, preeclampsia, placental abruption, and maternal anemia<sup>(7-10)</sup>.

MA can cross the placenta and enter the fetal bloodstream, and can be excreted in breast milk<sup>(11)</sup>. Fetal MA blood levels may increase the risk of various birth defects in infants, including defects of the fetal central nervous system, cardiovascular system, gastrointestinal system, and increase the risk of preterm birth, fetal growth restriction, low birth weight, and perinatal death<sup>(6,7,9,12)</sup>.

MA addiction can disrupt both central and peripheral immune responses, with changes in levels of inflammatory markers such as IL-6, IL-10, COX-2, TNF-alpha, and IL-1<sup>(13)</sup>. These alterations can exacerbate the disruption of B and T cell expression, macrophage and natural killer cell function, which can compromise the immune response<sup>(14,15)</sup>.

Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), systemic immune inflammation index (SII), the systemic inflammation response index (SIRI), and the aggregate index of systemic inflammation (AISI) are inflammatory ratios<sup>(16)</sup>. These biomarkers were used to predict the prognosis of various chronic conditions, such as pediatric infection-related conditions, cardiovascular diseases, malignancies, acute pancreatitis, autoimmune diseases, chronic obstructive pulmonary disease, and metabolic syndrome-related conditions<sup>(17)</sup>.

NLR, PLR, and SII are inexpensive determinants of inflammation, suitable for routine use, and easily calculated from complete blood count (CBC)<sup>(15,17)</sup>. In particular, SII is a marker that better indicates inflammation and immune response than NLR and PLR<sup>(15)</sup>.

Previous studies have found changes in inflammatory markers in individuals who use MA, such as increasing white blood cell (WBC) count, platelet count, NLR, PLR, MLR, and SII<sup>(15,18-22)</sup>. CBC is considered a routine laboratory test during prenatal care.

Therefore, this study was conducted to examine the complications that arise for both mothers and infants in pregnant women addicted to MA. This study was also conducted to investigate the relationship between inflammatory markers in MA abuse during pregnancy and to develop a screening tool for inflammatory markers potentially indicating MA use

in pregnant women.

## MATERIALS AND METHODS

This was a retrospective cohort study of pregnant women who gave birth at Nakhon Phanom Hospital (NPH). Data were collected from the medical records of women who delivered between January 2022 and December 2023. This study was approved by the Human Research Ethics Committee of NPH (NP-EC11-No.1/2567) in the year 2024.

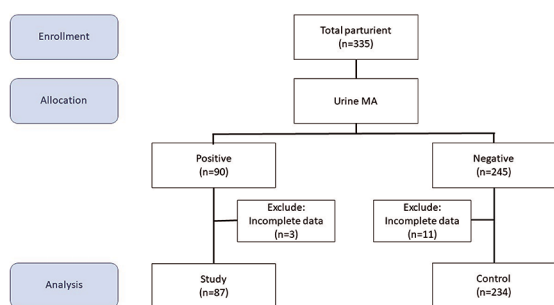
Subjects were parturients who delivered at NPH during the study period. Inclusion criteria were singleton pregnant women who delivered at NPH. All pregnant women obtained MA detection by a spot urine sample test. MA screening was conducted twice; the first one during antenatal care and the second one at admission for delivery. Spot urine samples were obtained for MA detection after consents were granted. Urine MA detection was performed by using a commercial kit (Meth Cassette rapid test kit, GPO, Bangkok, Thailand). This test kit employed a competitive binding immunochromatographic assay using monoclonal antibodies specific to MA. A positive result was indicated when the MA concentration in urine was equal to or greater than 1,000 ng/mL. Exclusion criteria was participant with congenital anomalies in the newborn.

Participants with positive urine MA (either at the first antenatal care visit or delivery room) were placed in the study group. The control group was subjects with negative urine MA test, who had similar general characteristics to those in the study group. Data included age, body mass index (BMI), gestational age (GA), educational status, occupation, income, parity, number of antenatal care visit and the latest CBC. The complicated outcomes of pregnancy were also collected.

NLR, PLR, and MLR were calculated by neutrophil, platelet, and monocyte count divided by lymphocyte count. SII was calculated by multiplying the number of neutrophils and platelets by the number of lymphocytes. SIRI was calculated by multiplying the number of neutrophils and monocytes by the number of lymphocytes. AISI was calculated by multiplying the platelet, neutrophil, and monocyte count, divided by the number of lymphocytes<sup>(16)</sup>.

Inflammatory marker namely NLR, PRL, MLR, SII, SIRI, and AISI, were calculated from the CBC report<sup>(16)</sup>. Significant inflammatory markers were used to make an equation for developing a screening tool (MA score) to indicate MA use in pregnant women.

Sample size was calculated using a formula based



**Figure 1.** Flow chart of the study and control group.

MA: methamphetamine, Positive: urine MA positive, Negative: urine MA negative

on the study by Wright et al<sup>(23)</sup>. Alpha and beta errors were set at levels of 0.05 and 0.2, respectively. The appropriate sample size was 82 cases in the study group and 221 cases in the control group. With an expected 10% sample loss, the final total participants were 90 cases in the study group and 245 cases in the control group.

Statistical analysis was computerized using Stata, version 12 (StataCorp LP, College Station, TX, USA). Continuous variables were analyzed by mean  $\pm$  standard deviation (SD) and Student's t-test. Chi-square test and Fisher's exact test were used for categorical data for an appropriate application. Statistical significance was determined by the probability value of less than 0.05 and 95% confidence interval (CI). The receiver operating characteristic (ROC) curve was used for evaluating the MA score.

## RESULTS

During the period of study, 87 and 234 pregnant women who gave birth at NPH had positive (study) and negative (control) urine MA test, respectively, as shown in **Figure 1**. The prevalence of MA use among pregnant women in this investigation was 2.4% (90/3803). The average age of participants was 27.5 years old. Average BMI was 27 kg/m<sup>2</sup>. Both groups had comparable age and BMI. Members of the study group had significantly lower GA, education level, monthly income, and number of antenatal care visits than those in the control group, as shown in **Table 1**. Members of the study group had a higher number of living children than the control group, with a statistically significant difference. Members of the study group had a higher risk of preterm labor than those in the control group (OR 5.7,  $p < 0.01$ ). Complications of pregnancy in both groups are presented in **Table 2**.

**Table 3** showed comparing CBC-derived inflammatory biomarkers and MA score among

**Table 1.** Baseline characteristics of pregnancy with MA (study) and non-MA (control)

	Study (n=87)	Control (n=234)	p-value
Age (years); mean $\pm$ SD	27.5 $\pm$ 5.8	27.5 $\pm$ 6.1	0.992
BMI (kg/m <sup>2</sup> ); mean $\pm$ SD	26.3 $\pm$ 4.6	27.3 $\pm$ 4.5	0.087
GA (weeks); mean $\pm$ SD	37.2 $\pm$ 2.0	38.3 $\pm$ 1.1	<0.001
Education; n (%)			<0.001
Primary	23 (26.4)	34 (14.5)	
Secondary	64 (73.6)	167 (71.4)	
Bachelor's or more	0 (0.0)	33 (14.1)	
Occupation; n (%)			<0.001
House wife	46 (52.9)	21 (9.0)	
Agriculture	16 (18.4)	49 (20.9)	
Employee	15 (17.2)	124 (53.0)	
Merchant	10 (11.5)	29 (12.4)	
Government officer	0 (0.0)	11 (4.7)	
Income (USD); n (%)			0.043
<298	46 (52.9)	88 (37.6)	
298-895	39 (44.8)	138 (59.0)	
>895	2 (2.3)	8 (3.4)	
Multiparity; n (%)	78 (89.7)	150 (64.1)	<0.001
ANC visit; mean $\pm$ SD	5.2 $\pm$ 3.5	11.3 $\pm$ 3.6	<0.001

MA=methamphetamine; SD=standard deviation  
1 USD=33.49 Thai Baht

**Table 2.** Complications of pregnancy among pregnancies with MA (study: n=87) and non-MA (control: n=234)

	n (%)		Odd ratio (95% CI)	p-value
	Study	Control		
GDM	0 (0.0)	17 (7.3)		
GHT	2 (2.3)	2 (0.9)	2.7 (0.4 to 19.7)	0.319
Preeclampsia	2 (2.3)	2 (0.9)	2.7 (0.4 to 19.7)	0.319
Abnormal presentation	2 (2.3)	2 (0.9)	2.7 (0.4 to 19.7)	0.319
PROM	7 (8.1)	12 (5.1)	1.6 (0.6 to 4.3)	0.329
Preterm Labor	13 (15.0)	7 (3.0)	5.7 (2.2 to 14.8)	<0.001
Poly/oligo-hydramnios	0 (0.0)	5 (2.1)	37.3 (4.8 to 291.5)	0.001
PPH	12 (13.8)	0 (0.0)		
Fetal distress	0 (0.0)	3 (1.3)		

GDM=gestational diabetes; GHT=gestational hypertension;  
PROM=premature rupture of membrane; PPH=postpartum hemorrhage;  
CI=confidence interval

pregnant mothers with MA and non-MA groups. Only NLR, PLR, MLR, and SII were significant prognostic factors. MLR in the MA group was lower than that in the control group. Meanwhile, NLR, PLR, and SII were higher in the MA group than in the control group.

A predictive model was generated and presented via our website. Meanwhile, NLR, PLR, MLR, and SII showed lower discriminatory abilities with area

**Table 3.** Comparing CBC-derived inflammatory biomarkers (NLR, PLR, MLR, SIRI, SII, AISI) and MA score among pregnancy with MA (study: n=87) and non-MA (control: n=234)

	OR (95% CI)		p-value	AuROC (95% CI)
	Study	Control		
NLR	4.44 (3.42 to 5.62)	3.98 (3.19 to 5.03)	0.033	57.76 (50.58 to 64.93)
PLR	150.18 (117.51 to 198.45)	121 (97.41 to 154.84)	<0.001	66.14 (59.27 to 73.01)
MLR	0.24 (0.2 to 0.33)	0.27 (0.22 to 0.35)	0.040	42.54 (35.34 to 49.75)
SIRI	2.02 (1.43 to 3.31)	2.24 (1.56 to 3.16)	0.532	47.73 (40.26 to 55.20)
SII	1,268.66 (896.45 to 1,787.05)	1,028.04 (750.48 to 1,253.45)	<0.001	65.81 (58.81 to 72.80)
AISI	655.17 (399.88 to 969.86)	556.53 (365.79 to 794.26)	0.128	55.53 (48.03 to 63.02)

NLR=neutrophil/lymphocyte ratio; PLR=platelet/lymphocyte ratio; MLR=monocyte counts/lymphocyte counts; SIRI=systemic inflammation response index [(neutrophil counts\*monocyte counts)/lymphocyte counts]; SII=systemic immune inflammation index [(platelet counts\*neutrophil counts)/lymphocyte counts]; AISI=aggregate index of systemic inflammation [(platelet counts\*neutrophil counts\*monocyte counts)/lymphocyte counts], AuROC=area under the receiver operating characteristic; CI=confidence interval; MA=methamphetamine

**Table 4.** Distribution of study and control according to MA scores into low, moderate, and high probabilities

MA score	n (%)		LR+	95% CI	p-value
	Study	Control			
Low: < -0.5	33 (37.9)	177 (75.6)	0.50	0.31 to 0.78	0.002
Moderate: -0.5 to 2.25	46 (52.9)	57 (24.4)	2.17	1.33 to 3.52	0.001
High: >2.25	8 (9.2)	0 (0.0)	21.52	2.79 to 958.54	<0.001

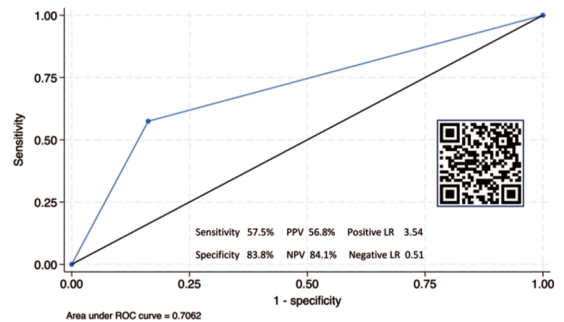
MA=methamphetamine; LR+=positive likelihood ratio of positive; CI=confidence interval  
Study: Urine MA positive, Control: Urine MA negative

under the ROC curve (AuROC) values of 57.8%, 66.1%, 42.5%, and 65.8%, respectively. MA score were calculated from  $-1.165 + [(-0.308 \cdot \text{NLR}) + (0.008 \cdot \text{PLR}) + (-5.863 \cdot \text{MLR}) + (0.002 \cdot \text{SII})]$  as calculated from <https://pailin-ma-score.vercel.app/> or QR code as shown in Figure 2. Analysis of the AuROC demonstrated that the MA score had the best discriminatory ability between the two groups, with an AuROC of 70.6% (95% CI 64.9 to 76.4).

Subjects were categorized into three groups based on the probability of MA detection: low (MA score < -0.5), moderate (MA score between -0.5 and 2.25), and high (MA score >2.25). The positive likelihood ratio (LR+) in low, moderate, and high-probability groups was 0.5 (95% CI 0.3 to 0.8), 2.2 (95% CI 1.3 to 3.5), and 21.5 (95% CI 2.8 to 958.5), respectively, with significant positive correlation ( $p < 0.001$ ) as shown in Table 4.

The analysis of the relationship between MA scores and the risk of detecting MA in urine revealed a positive correlation. The performance evaluation of the prediction model using calibration techniques was presented in the form of a calibration plot, which was a statistical method used to assess model accuracy, as shown in Figure 3.

Overall MA score demonstrated a sensitivity, specificity, positive predictive value (PPV), and



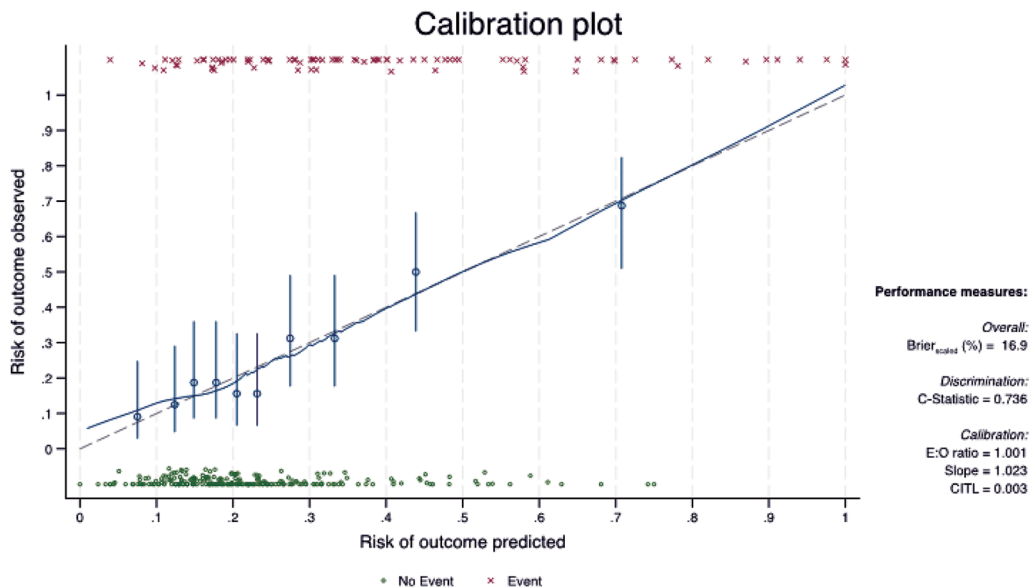
**Figure 2.** Area under the receiver operating characteristic curve of the MA score and 95% confidence interval on the prediction of urine methamphetamine positivity.

MA: methamphetamine

negative predictive value (NPV) of 57.5%, 83.8%, 56.8%, and 84.1%, respectively. The positive and negative likelihood ratios were 3.5 and 0.5, respectively.

**DISCUSSION**

From this study, the prevalence of MA use in pregnancy was 2.4%, higher than previous studies that revealed 0.79% and 1.28%<sup>(8,10)</sup>. The prevalence might be higher due to the study area. Premchit conducted her study in pregnant women who attended and delivered at a hospital in the northern part of Bangkok<sup>(8)</sup>.



**Figure 3.** Calibration plot.

MA: methamphetamine, predicted outcome (MA score), observed outcome (urine MA)

Homsup et al. conducted the study in the central part of Bangkok<sup>(10)</sup>. The current study was set in a rural area bordering a section (the Northeastern region of Thailand) where MA is highly prevalent. Maternal and neonatal complications incidences were higher in the MA group, especially in the incidence of preterm labor, which was consistent with results from previous studies<sup>(8-10,24)</sup>.

This study compared inflammatory markers in those who used MA during pregnancy and those who did not. The study found a significant increase in NLR, similar to Taiwanese and Turkish studies<sup>(15,21)</sup>. Another Turkish study also showed an increase in NLR, although not significant<sup>(14)</sup>. Increases in PLR and SII were also found in other studies<sup>(15,21,22)</sup>. Meanwhile, a decrease in MLR was present in this study, but increases were found in other studies<sup>(14,21)</sup>. The differences in inflammatory marker levels across studies might be due to factors affecting WBC and platelet levels. This study was conducted in pregnant individuals. Physiological changes during pregnancy cause increased WBCs, neutrophils, and monocytes, and decreased lymphocytes and platelets<sup>(25,26)</sup>. This is why the profile of inflammatory markers in pregnant women might differ from normal levels. Other factors affecting inflammation included exercise, obesity, smoking, alcohol intake, high altitude, air pollution, and sleep deprivation<sup>(27)</sup>. From the results of the present logistic regression analysis, four inflammatory markers were chosen to establish an MA score.

The significant inflammatory markers were applied and generated to formula by statistic model as shown in Table 3. Appropriate cut off point of the MA score was chosen at a level of  $-1.175$  that sensitivity, specificity, PPV, and NPV of 57.5%, 83.8%, 56.8%, and 84.1%, respectively.

The MA score should be a good tool to estimate the probability of MA use in pregnancy. It could help medical personnel make decisions regarding further investigation, such as urine amphetamine testing. This score was calculated by CBC, a test all pregnant women must undergo before antenatal care. This MA score should be used to screen all pregnant women in areas with a low prevalence of MA addiction.

However, there was no reason to perform urine MA in all pregnant women. In the institute that found a high prevalence of MA in pregnant women, the standard urine MA should be performed in all expectant mothers. In markedly suspected MA use, although urine MA was negative, a high MA score was obtained. The urine MA test must be repeated carefully. The limitation of this study was its single-center setting and retrospective design, which might not be representative of all pregnant women. Lack of preexisting data on MA usage in pregnancy might affect the sample size calculation and accuracy of the preliminary screening tool. Moreover, many factors might have affected inflammatory markers. Nevertheless, this study was easy to calculate the probability of MA using MA scores in pregnancy. Modifications and applications

should be developed in the future. The other strength in this study was that it was conducted in a high prevalence of MA addiction<sup>(3,4)</sup>. All pregnant women underwent urine analysis for MA.

### CONCLUSION

MA could affect user health and social conditions, especially in pregnant women. This study found that MA usage directly affected both the mother and fetus. MA screening was important to prevent complications. Inflammatory markers were found to be associated with MA addiction. The MA score was calculated from NLR, PLR, MLR, and SII. The sensitivity, specificity, PPV, and NPV were 57.5%, 83.8%, 56.8%, and 84.1%, respectively.

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### Authors' contribution

PK and PP: Conceptualization and methodology; PK and PP: Investigation; PK and PP: Analysis; PK and PP: Visualization and writing-original draft; PP, KB, and KS: Writing-review and editing; KS: Supervision. All authors have read and agreed to the final version of the manuscript.

### Clinical trial registration

There was no clinical trial registration due to retrospective design.

### Conflicts of interest

The authors declare no conflicts of interest.

### Data availability statement

The data that support the findings of this study are not openly available and are available from the corresponding author upon reasonable request.

### Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of NPH (NP-EC11-No.1/2567) in the year 2024.

### Use of artificial intelligence

No generative AI was used in the preparation of this manuscript.

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