

# ARTICLE

# ASSOCIATION AMONG TIMING OF FIRST VISIT, ANTENATAL CARE FREQUENCY, AND ANAEMIA GRAVIDARUM DURING THE PEAK PERIOD OF THE COVID-19 PANDEMIC

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#### ABSTRACT

Anaemia gravidarum is a health problem that affects pregnancy outcomes. Antenatal care is an effort to screen highrisk pregnancies to provide earlier appropriate management. In 2021, the pandemic forced people to limit their activities, including antenatal care (ANC) visits. The study aimed to explain the association among the timing of the first visit, ANC frequency, and incidence of anaemia gravidarum. The case-control study used the medical record data from Puskesmas Godean 2. The subjects were 30 pregnant women with anaemia in the case group and 30 nonanaemic pregnant women in the control group. The dependent variable was the incidence of anaemia gravidarum. Other variables included age, occupation, and education of the mother, partner's education, parity status, pregnancy spacing, nutritional status, and history of comorbidities. The chi-square and logistic regression were used to analyse the data. It was found that ANC frequency of less than four times and first visit (K1) after passing the first trimester of gestational age increased the risk of anaemia gravidarum (p-value <0.05). Efforts to increase awareness of the importance of immediate first ANC visit and frequency of ANC visits need to be made to reduce the risk of anaemia gravidarum.

Keywords: Anaemia gravidarum, ANC frequency, antenatal care, timing of first visit

#### АБСТРАКТ

Анемия gravidarum - это проблема здравоохранения, которая влияет на исход беременности у матерей и детей. Дородовой уход - это попытка выявить беременность с высоким риском, включая анемию, чтобы обеспечить соответствующее лечение на ранней стадии. В 2021 году пандемическая ситуация заставила людей ограничить свою деятельность, включая посещение медицинских учреждений. Целью исследования было объяснить взаимосвязь между посещениями АНК и частотой возникновения анемии gravidarum. В данном контрольном исследовании использовались данные медицинских карт из Puskesmas Godean 2. Испытуемые состояли из 30 беременных женщин с анемией в контрольной группе и 30 женщин без анемии в контрольной группе. Зависимой переменной была частота встречаемости анемии gravidarum. Посещения АНК включали частоту и время первого посещения (К1). Другие переменные включали возраст матери, род занятий матери, образование матери и партнера, паритетный статус, интервал между беременностями, состояние питания и наличие сопутствующих заболеваний. При анализе данных использовались тест хиквадрат и логистическая регрессия. Данные показали, что частота проведения АНК менее четырех раз и первый визит (К1) после первого триместра беременности увеличивали риск развития анемии gravidarum Для снижения риска анемии gravidarum необходимы усилия по повышению (p-value <0,05). осведомленности о необходимости проведения первого посещения АНК как можно раньше и увеличению частоты посещений АНК.

Ключевые слова: анемия гравидарум, частота АНК, дородовый уход, время первого посещения

# **INTRODUCTION**

The coronavirus disease 2019 (COVID-19) pandemic has affected various aspects of life, especially health(1). To suppress the spread of the disease, the Indonesian government implemented the Large-Scale Social Restrictions (PSBB) policy. This effort had an impact on access to health services. Health workers and facilities concentrated on handling COVID-19 cases which peaked in 2021. Health facilities, including community health centres (Puskesmas), focused more on managing COVID-19 cases. The high number of COVID-19 cases handled by health facilities had made Puskesmas, clinics, and hospitals become effective disease transmission sites. Therefore, the public was encouraged to visit health facilities only for urgent need, and it was advisable to utilize online consultation media (2).

Meanwhile, antenatal care (ANC) is a government program that aims to routinely monitor the health condition of mother and foetus during pregnancy. The program also aims to identify high-risk pregnancies (screening) and prevent further pregnancy complications. With early detection. appropriate treatment of health problems in pregnancy is expected to be provided. Therefore, ANC check-ups should be carried out as early as possible and on a regular basis (3). The COVID-19 pandemic in Indonesia, which continued to increase in 2021, has also affected maternal and neonatal health services in terms of quantity and quality. Pregnant women were one of the groups that was vulnerable to the impact of the COVID-19 pandemic. In addition, their visits to health facilities tended to be limited. On the one hand, a decrease in the frequency of visits by healthy pregnant women to health facilities and restrictions on contact with health workers were expected to reduce the risk of COVID-19 transmission. On the other hand, it was feared that this could increase maternal and child morbidity and mortality from other causes (4,5).

Anaemia remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide (6). The health profile of Yogyakarta City in 2020 indicated that the incidence of anaemia in pregnant women fluctuated from 2016 to 2020. Data from the Health Office of Yogyakarta Province show that in 2020 the anaemia rate increased to 15.84% (7). The causes of anaemia are multifactorial, including infectious diseases and deficiency in such micronutrients as iron, folic acid, vitamin A, and vitamin B12. Anaemia gravidarum is often found in underdeveloped regions with a high poverty rate, poor nutritional status, unhygienic environment, low level of education, and unemployment. Lack of health facilities and poor understanding of the importance of antenatal visits are also risk factors in *aravidarum* (8). Anaemia anaemia in pregnancy can increase the risk of uterine atony, peripartum haemorrhage, low birth weight, premature birth, and even death. Appropriate interventions carried out during antenatal care are expected to decrease the prevalence of anaemia in the third trimester which will correspondingly reduce the risk to the mother and child (9).

It is necessary to prevent and treat anaemia in pregnant women. On the other hand, research shows a decrease in ANC visits during the COVID-19 pandemic (10). This study aims to determine the correlation between pregnancy visits and the incidence of *anaemia gravidarum* during 2021, which was the peak period of the COVID-19 pandemic.

## MATERIAL AND METHODS

The study used a case-control design. The population was pregnant women who received ANC at Puskesmas Godean 2 in Sleman Regency over the period of January 1, 2021 - December 31, 2021, documented in the online-based medical records and records of pregnant women who made ANC visits to Puskesmas. The subjects were divided into two groups. The case group consisted of pregnant women with *anaemia gravidarum*, while the control group was those without anaemia gravidarum. Throughout 2021, there were 87 mothers with anaemia among a total of 486 pregnant women at Puskesmas Godean 2. Of this number, 31 had incomplete medical record data, and 26 still needed to follow up on ANC visits to Puskesmas Godean 2. The sample size for each group was 30 people, which was based on the results of the minimum sample size calculation for the hypothesis testing of two proportions in two independent groups.

The ANC visits in this study included the number of visits and the gestational age at the first ANC visit (K1). The other variables were the maternal age, maternal occupation, mother's education, parity status, pregnancy spacing, nutritional status, and history of comorbidities. The nutritional status was determined based on the mid-upper arm circumference (MUAC) of < 23.5 cm and  $\ge 23.5$ cm. The frequency of ANC visits was categorized into less than four and four or more visits. The time of the first ANC visit was the mother's gestational age when she came to Puskesmas for the first time for ANC, which was divided into within the first trimester and beyond the first trimester. The dependent variable was the anaemia status of the pregnant women. The mother was grouped into anaemic if the haemoglobin (Hb) level was <11 gr/dL and not anaemic if Hb >11 gr/dL. The data were collected in July 2022 after obtaining ethical approval from the Research and Health Ethics Committee of the Faculty of Medicine of Universitas Islam Indonesia. No. with letter 10/Ka.Kom.Et/70/KE/VII/2022, as well as permission from Puskesmas Godean 2 in Sleman Regency. A bivariate analysis was carried out by using a chi-square test to determine the relationship between the independent variables and the dependent variable. In addition, a multivariate analysis was performed by using logistic regression. The significance of the correlation was declared meaningful if the p-value was less than 0.05.

# RESULT

The data showed that most of the pregnant women in the case and control groups were 20-35 years old, worked as housewives (not working), and were high school graduates. The mothers in the case group were mostly multiparous (60%), which differed from the control group where most were primiparous (53.3%). In both of the case and control groups, the majority of the mothers had four or more ANC visits. The difference was in the timing of the first ANC visit (K1), most of which was made after the first trimester in the anaemia group (86.7%). In contrast, in the non-anaemia group, K1 was primarily made in the first trimester (66.7%). The complete description of the characteristics of the research subjects is presented in Table 1. The results of the bivariable analysis showed that the incidence of *anaemia gravidarum* was not associated with maternal age, maternal employment, mother's education, parity, pregnancy spacing, and nutritional status (pvalue > 0.05). The incidence of anaemia gravidarum correlated with ANC frequency and gestational age at the time of the first ANC visit (K1). Women who had less than four ANC visits had 10.7 times more risk of anaemia compared to those with four or more ANC visits (p-value = 0.001; 95% CI = 2.15-53.35). Pregnant women who made their first ANC visit at more than 12 weeks of gestational age (beyond the first trimester) had a 13-fold risk of anaemia as opposed to those making their first ANC visit within the first trimester (pvalue = 0.000; 95% CI = 3.55-47.59).

Variable	Category	Case Group		Control Group	
		N	%	n	%
	<20	2	6.7	2	6.7
Mother's age (years)	20-35	23	76.7	24	80.0
Hould buge (Jourb)	>35	5	16.7	4	13.3
Mother's Occupation	Employed	7	23.3	13	43.3
	unemployed	23	76.7	17	56.7
	Elementary School	0	0	2	6.7
	Junior High School	10	33.3	7	23.3
Mother's Last Education	Senior High Scool	17	56.7	19	63.3
	Higher Education	3	10.0	2	6.7
	Primiparos	11	36.7	16	53.3
Parity	Multiparous	18	60	13	43.3
-	Grande Multipara	1	3.3	1	3.3
Pregnancy	Never giving birth	11	36.7	16	53.3
Spacing	1-23 months	3	10	0	0
	≥24 months	16	53.3	14	46.7
Nutritional Status Comorbidities	MUAC <23.5 cm	11	36.7	7	23.3
	MUAC ≥23.5 cm	19	63.3	23	76.7
	One or more	6	20	3	10.0
	None	24	80.0	27	90.0
ANC Frequency	<4	13	43.3	2	6.7
	≥4	17	56.7	28	92.3
Timing of first ANC visit (K1)	Late (beyond 1 <sup>st</sup> Trimester)	26	86.7	10	33.3
	Early (1 <sup>st</sup> Trimester)	4	13.3	20	66.7

# Table 1. Characteristics of the Case Group (Anaemia) and Control Group (Non-Anaemia)

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Variable	Category	P value	OR
Mother's age (years)	At Risk	0.754	1.21
	Not a Risk		
Mother's Occupation	Employed	0.100	2.51
	Unemployed		
Mother's Education	≤Junior High School	0.781	1.17
	>Junior High School		
Parity	Primiparos	0.194	0.51
	≥Multiparous		
Pregnancy spacing in	<2 Years	0.244	1.88
multiparous	≥ 2 Years		
Nutritional Status	MUAC <23.5 cm	0.260	1.90
Comorbidities	MUAC ≥23.5 cm		
Frequency of ANC visi Time	<4	0.111*	10.7
of	≥4		
(K1)	Late	0.000*	13.0
	Early		

\*P-value < 0.05

Table 3 shows the results of the multivariate analysis of several variables that might affect the incidence of *anaemia gravidarum* at Puskesmas Godean 2. Two variables associated with the incidence of anaemia were the frequency of ANC and the timing of the first ANC visit. The pregnant women with a frequency of ANC visits of less than four times had 8.62 times higher risk of **Table 3.** Results of Multivariate Analysis of the first anal

anaemia compared to those with four or more visits (p-value 0.023). In addition, the timing of the first ANC visit (K1) also had significant association with the incidence of *anaemia gravidarum* (p-value = 0.001). The pregnant women with the first ANC visit after the first trimester had 12.8 times greater risk of developing anaemia than those who made the first ANC visit during the first trimester.

**Table 3.** Results of Multivariate Analysis of the Factors Affecting the Incidence of Anaemia

 Gravidarum

Variable	P-value	OR	95%Cl	
Mother's age	0.132	4.6	0.63-33.66	
Mother's Occupation	0.896	1.1	0.23-5.49	
Mother's Education	0.753	0.8	0.17-3.56	
Nutritional Status	0.597	1.5	0.31-7.60	
ANC Frequency	0.023*	8.6	1.35-54.96	
K1 Time	0.001*	12.8	2.89-56.96	

\*P-value < 0.05

## DISCUSSION

The COVID-19 pandemic has greatly affected health services. Research shows decreased ANC visits in poor and developing countries during the pandemic. Pregnancy and delivery outcomes were also worse compared to before the pandemic, whereas mothers and children became vulnerable groups. The pandemic also affected people's behaviour in accessing health services. On the other hand, the global prevalence of anaemia in pregnant women remains high, particularly in developing countries. Iron deficiency anaemia is the most common type of anaemia experienced by pregnant women. Data from the Health Office of Yogyakarta Special Region shows that from 2016 to 2020 the incidence of anaemia had increased. The percentage of anaemia in pregnant women at Puskesmas Godean 2 was 14.2% in 2020 and 18.2% in 2021.

The frequency of ANC and the timing of the first ANC visit influence the incidence of *anaemia gravidarum*. The results of this study is in accordance with the findings of research in Nepal (11) which found that the low

frequency of ANC visits (<4 times) had a significant correlation with the incidence of anaemia gravidarum. The risk of anaemia in pregnant women with <4 ANC visits in Nepal was 2.28 times greater compared to those who had 4 times or more visits (p-value <0.001). A study in Kediri showed that regularity of ANC could affect the incidence of anaemia (p-value = 0.004). Mothers who did not regularly perform ANC had 6.34 times risk of experiencing more anaemia gravidarum compared to those who did (12). It is recommended that pregnant women receive antenatal care at least four times during pregnancy (K4), including at least once each in the first and second trimesters and twice in the third trimester. Compliance with ANC visits is defined as the adherence of pregnant women to visiting health care facilities at least four times during pregnancy. At the time of ANC, the mother will receive various information and education related to pregnancy and early preparation for childbirth (5).

ANC is one of the efforts to reduce maternal and neonatal mortality (1,4). The service standards during ANC include measurement of the weight, height, and blood pressure, determination of the nutritional fundus uteri height, foetal status, presentation, and foetal heart rate, screening of the Tetanus Toxoid (TT) immunization status, administration of iron tablets and simple lab tests, management of cases, and counselling(4). The counselling includes nutrition counselling, childbirth planning, breastfeeding, and family planning. ANC is useful for reducing the risk of anaemia. Pregnant women who do not attend ANC may not receive iron tablets and nutritional counselling, which are essential to address anaemia. Consequently, the treatment they receive may be too late if signs of a high-risk pregnancy occur. Maternal non-compliance with taking iron tablets is one of the factors that affects the mother's Haemoglobin level. Pregnant women who do not receive regular ANC by standards (at least four visits) will not benefit from optimal antenatal care, including a lack of iron tablet administration. They are also more prone to infections and late recognition of high-risk pregnancy. The adequacy of ANC visits has shown to affect maternal and child outcomes, including low birth weight in babies and perinatal mortality(13). In summary, three essential aspects to fulfil regarding ANC include the timing of the first visit in early pregnancy, the frequency of ANC of at least four times, and the provision of quality ANC services (14).

However, Indonesia still faces significant challenges, including maternal mortality and neonatal mortality. This condition needs particular attention considering that pregnant women, maternity, postpartum, and newborn babies are vulnerable to COVID-19 infection. It is feared that this condition can further increase mortality and morbidity in mothers or babies. COVID-19 has significantly affected various aspects of life such as health services since routine-service restrictions, including for maternal and infant health services, have been imposed to prevent virus transmission (15).

Aziz et al. (2020) suggested some modifications to antenatal care during the

COVID-19 pandemic that are needed to help pregnant women perform social distancing to reduce the transmission of Corona virus among pregnant women, staff, and visitors in health facilities. One of the modifications states that physical antenatal care is conducted at least six times for low-risk pregnant women. However, in the case of high-risk pregnancies, the frequency of direct consultation can be adjusted. The latest guidelines recommend that antenatal checkups during pregnancy are done six times, in which visits are made twice in the first trimester, once in the second trimester, and three times in the third trimester (4). In addition, online education is one of the alternatives to overcome the problem of limited information received by pregnant women due to a lack of face-to-face contact with health workers (2). However, several parts of ANC examination remain necessary to be conducted in person with a health worker. Research by Subiyatin and Revinel (2021) described the incidence of anaemia among pregnant women during the COVID-19 pandemic. The results showed that the incidence of anaemia was unrelated to the ANC frequency (p-value = 0.743), and most of these pregnant women continued to make antenatal visits during the COVID-19 pandemic by following the health service standards(16).

Meanwhile, most of the pregnant women in this study made fewer than six visits as the latest standards of antenatal care during the COVID-19 pandemic. Previous researchers stated that the number of ANC visits is influenced by such factors as the mother's age during pregnancy, husband's occupation, mother's educational attainment, and number of visits (17). In addition, the number of ANC visits is affected by the age of the mother during pregnancy, husband's occupation, mother's education level(17), distance of residence to health facilities, family income, family support, quality of health services, and government policies related to the large-scale social restrictions (PSBB)(18). Pangastuti (2020) stated that the correlation between ANC coverage and the incidence of anaemia among pregnant women in East Java is very weak. It may be due to the unequal training of ANC services for midwives. In addition, not all midwives comply with the established antenatal service standards. Another influential factor is the inadequate facilities and infrastructure for ANC services which below standard(19). То remain date. Indonesia still needs to address the problem of disparities in ANC coverage. Research revealed that the lowest coverage is found in Maluku Province and Papua Province (20).

Data showed that 36 (60%) pregnant women made their first ANC visit (K1) late or after the first trimester. Meanwhile, based on the data from the 2018 Indonesian Basic Health Survey, 90% pregnant women made at least one ANC visit, and 80% made their first ANC visit in the first trimester (21). This study also revealed a statistically significant correlation between the timing of K1 visit and the incidence of anaemia among pregnant women at Puskesmas Godean 2 (p-value = 0.000). The pregnant women who made their first ANC visit after the first trimester (late) had a higher risk than those who made it earlier (p<0.05). Other studies also showed similar results to this finding (p-value < 0.05) (22, 23).

The timing of ANC visits plays a vital role in anaemia management. The earlier the K1 visit is made in the first trimester, the earlier the pregnant woman will receive folic acid supplements, iron supplements, or other nutrients needed during pregnancy and education for the mother. essential Haemoglobin (Hb) measurement in early pregnancy also enables anaemia to be detected more immediately, thereby allowing earlier management. Taking iron supplements for at least 90 days is expected to increase the Hb level of pregnant women. Since deficiencies of micronutrients such as iron, folate, and vitamin B12 before and during pregnancy will increase a woman's risk of anaemia, fulfilling the intake of these nutrients is crucial during this critical phase of her life. The earlier the intake, the better the

effect on the health of the mother and foetus (6).

Several interventions can be carried out to increase K1 coverage, including mentoring programmes for prospective mothers (21). Concern for the nutrition of pregnant women and ANC will increase the mothers' motivation to make efforts to meet their needs and those of their foetuses. It can also reduce the incidence of anaemia in the third trimester of pregnancy or before childbirth (9). Research in Ghana showed that although there is a general increase in the frequency of visits (more than four times), many women remain late for their first visit. Poor quality ANC and inadequate ANC increase the risk of anaemia. Early and regular ANC visits allow women to receive the necessary facilities and services(14).

This study also analysed the association of several other factors with the incidence of anaemia, including age, education, occupation, pregnancy spacing, parity, nutritional status, and maternal comorbidity history. The results of this study indicated that there was no significant relationship between maternal age and the incidence of anaemia gravidarum (pvalue = 0.132). Different results were obtained in research conducted by Vionalita and Permata (2020), which showed a significant relationship between maternal age and the incidence of anaemia (p-value = 0.037) (24). However, the results of this study follow other studies which suggested that maternal age did not affect the incidence of anaemia (p-value>0.05) (11,25). The study also mentioned that mothers in the at-risk age group (less than 20 years or more than 35 years) already have adequate nutritional status or sufficient nutrition. The same condition is likely to occur in this study. Pregnant women generally need more nutrients for their bodies and foetuses to achieve optimal growth. Therefore, meeting these needs can reduce the risk of anaemia gravidarum.

In this study, the educational attainment of forty-seven mothers (78.3%) was high school and above. This shows that the incidence of

anaemia gravidarum is not associated with the mother's education level. Another study showed the same finding (p-value = (0.153)(16). On the other hand, a study in Nepal found that mothers with a low education level had 2.8 times greater risk of developing anaemia compared to those with higher education level (p-value < 0.001) (11). Highly educated pregnant women can gain more knowledge or access information about pregnancy better than those with low education level. In addition, their level of alertness and awareness of their body's health is also greater. This condition will affect their attitude or behaviour. Furthermore, they usuallv have а better socioeconomic background which allow them to receive better nutritional intake.

The results showed no correlation between employment and the incidence of anaemia (p-value >0.05). According to some studies, employment status determines a person's economic status. Working pregnant women tend to have a higher income for daily needs, fulfilling their including nutritional needs during pregnancy (12,26,27). Meanwhile, research conducted by Bansal et al. (2020) showed the opposite as the incidence of anaemia in pregnant women is experienced more by those who work. Working makes a mother need more nutritional intake, and they experience physical fatigue more easily (28). Furthermore, working causes mothers to have insufficient time to rest and make ANC visits. This study showed that 10% or three anaemic pregnant women at Puskesmas Godean 2 had a pregnancy interval of fewer than two years. The parity status in this study had no relationship with the incidence of anaemia (pvalue = 0.194). This result aligns with the studies by Aznam and Inayati (2020) as well as by Pusporini et al. (2021) (25,29). However, this finding is different from the research conducted by Vionalita and Permata which found that multiparous (2020).mothers had 3.9 times greater risk of developing anaemia than primiparous mothers (24). Anaemia in pregnancy often

occurs in mothers with multiparity and close spacing of pregnancies due to a lack of pregnancy planning in the family (30). The prevalence of anaemia tends to increase in mothers with close pregnancy spacing. It is associated with the theory that maternal iron stores can decrease during consecutive pregnancies while it takes at least two years for the body to restore iron reserves as in normal conditions.

In this study, nutritional status had no significant relationship with the incidence of anaemia (p-value = 0.260). This result is in line with a study conducted in South Sulawesi (31). In contrast, Pusporini et al. (2021) stated that pregnant women with Chronic Energy Deficiency (CED) at Puskesmas Singgani had 24 times greater risk of developing anaemia compared to those without CED (29). The condition of CED occurs when the body lacks macronutrients during a specific period, which is seen from the upper arm circumference size of less than 23.5 cm. A meta-analysis study showed that CED is a significant factor in maternal anaemia (32). Adequate amounts of macronutrients and micronutrients play an essential role during pregnancy to supply the maternal and foetal nutrient demands; consequently, a lack of nutritional intake in pregnant women with CED can lead to anaemia.

In this study, 51 pregnant women (85%) did not have a history of comorbid diseases or comorbidities during pregnancy. Meanwhile, the comorbidities found in this study were hypertension and urinary tract infection. The analysis shows no significant correlation between comorbidities and the incidence of anaemia. However, Bansal et al. (2020) stated that there was a significant relationship between the presence of comorbid diseases and the incidence of anaemia (p-value = 0.001). The study also suggested that anaemia is more significant in patients with one or more comorbidities, such as hypertension, diabetes, and hypothyroidism (28).

Meanwhile, studies by Mahyuni et al. (2019) and Zuiatna (2021) mentioned that *anaemia gravidarum* was not associated with infectious diseases in pregnant women at Puskesmas Kebon Jeruk and Pasungkan (33). The infectious diseases referred to in their studies were diarrhoea, tuberculosis, and helminth infection (34). The incidence of anaemia is six times more frequent in pregnant women with a history of worm infections because such infections cause loss of appetite and impaired absorption of nutrients. Chronic bleeding leads to iron loss while iron is an essential micronutrient for almost all living cells. During infection, invading pathogens and host cells need iron to maintain their function, metabolism, and proliferation. In most pathogens, microbial iron uptake is related to their virulence. On the other hand, iron uptake from bacteria and other microorganisms is an efficient host defence strategy in line with the principles of 'nutritional immunity' (35).

# CONCLUSION

The frequency of ANC visits during pregnancy and the timing of the first visit (K1) are essential factors in anaemia gravidarum. Pregnant women with less than 4 ANC visits had 8.6 times higher risk of anaemia gravidarum compared to those with four or more visits. Pregnant women who had their first visit beyond the first trimester of pregnancy had 12.8 times greater risk compared to those who had their first visit in the first trimester. Efforts to prevent anaemia *aravidarum* should be sustainably made by providing information, motivation, and encouragement for pregnant women to take ANC examinations in accordance with the guidelines, which are at least four times during pregnancy. In addition, pregnant women are strongly encouraged to take the first ANC examination as early as possible, or in the first trimester.

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## DECLARATIONS

All authors listed on the title page have contributed significantly to the work, have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to submission.

There are no conflict of interest.

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