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Usefulness of Anti-Müllerian Hormone to Predict Outcomes of Threatened Miscarriage in Naturally Conceived Pregnancies

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ABSTRACT
Background: Anti-Müllerian hormone (AMH) levels fluctuate in a complicated and not always one-way fashion in the early stages of pregnancy. An abundance of research has looked at how AMH levels correlate with various pregnancy problems.
Objective: To determine the association between AMH and miscarriage among women naturally conceived pregnancy.
Methods: Total of 40 pregnant women at gestational age ranged between 6-8 weeks who had first trimester threatened miscarriage while they were trying for naturally conceive were included in our prospective cohort study at Obstetrics and Gynecology Department at Fetomaternal Unit in Zagazig University Hospital. All patients were subjected to assay serum AMH.
Results: Anti-Möllerian hormone (AMH) among the studied cases ranged from 0.8 to 4 ng/ml with mean 2.41 ng/ml and median 2.55 ng/ml. Statistical analysis revealed a negative connection between AMH and age and statistical +ve significant correlation between AMH and gestational sac size, crown lump length, yolk sac size and fetal heart rate among the studied cases. There was a statistically significant decrease in AMH among cases had aborted before 20 weeks compared to cases completed pregnancy. AMH at cut off <1.9 ng/ml had sensitivity 85.7%, specificity 87.9% and accuracy 87.5% in prediction of early pregnancy loss among the studied cases.
Conclusion: Ovarian reserve may be accurately measured by measuring anti-Müllerian hormone levels in the blood. However, findings on the significance of AMH level in making pregnancy predictions are inconsistent. The likelihood of having a miscarriage is inversely related to AMH levels. Miscarriages are more common among women who have substantially decreased ovarian reserve.
Keywords: Anti-Müllerian Hormone, Naturally Conceived Pregnancies.

INTRODUCTION
About a quarter of all pregnancies have bleeding in the first trimester, making it one of the most frequent obstetric problems. When vaginal bleeding or discharge occurs during the early half of pregnancy and the cervical os is closed, a miscarriage is suspected [1]. When a pregnancy ends, but the products of conception are not immediately expelled, a doctor will diagnose a missed abortion (MA). As an early-pregnancy problem, MA affects around 15% of all pregnancies that are formally documented [2]. Several variables have been identified as contributors to this epidemic, including advanced maternal age (often over 35), a history of miscarriage, chronic stress, uterine anatomical abnormalities (such as adhesions or tumors), and substance abuse (including tobacco, alcohol, and certain narcotics) [3].

When assessing a possible early pregnancy or missed miscarriage, transvaginal ultrasonography is the most crucial diagnostic tool [4].

Serum and ultrasound ovarian reserve markers have been extensively researched in infertile populations, and both have demonstrated efficacy in the quantitative measurement of ovarian reserve [5]. There is, however, no definitive indicator of oocyte quality.

The size and structure of the gestational sac and the embryo-fetus can vary, which has been the subject of research into why some pregnancies end in miscarriage. However, the yolk sac (YS), the first component within the gestational sac seen on ultrasonography, has been

examined far less extensively. The YS often presents as a spherical structure with an anechoic core and a regular, well-defined, anechogenic rim. Before placental circulation develops, it serves as the major pathway for fetal to mother communication [6]. Nutrition, metabolism, hematopoiesis, endocrine, and immunologic roles are all played by it in the developing embryo. **Bagratee et al.** [7] determine the baseline YS size, which climbs to a peak between weeks 10 and 11, then declines.

After 10 weeks of pregnancy, the crown rump measures 87 mm, and at 12 weeks it measures 120 mm[8]. At 8 weeks of age or fewer, an embryo with a heart rate (HER) of less than 100 beats per minute was considered to be sluggish[9].

Follicle granulosa cells in the pre-antral and early antral stages secrete a hormone called anti-müllerian hormone (AMH). Due to its function as a measure of oocyte number, AMH naturally falls with age[10]. Oocyte yield after ovarian hyperstimulation can be predicted, as can the age of menopause, using AMH. However, it is still unclear if AMH may be utilised as a potential diagnostic of oocyte quality[11].

Studies have shown that AMH levels do not change during pregnancy. Serum AMH levels fluctuate non-significantly among pregnant women, with the biggest peaks or troughs reported between 4 and 7 weeks of gestation. This finding suggests that variations in AMH

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levels in early pregnancy are complex and not always unidirectional[12].

As more and more women put off having children, there has been a rise in the number of questions asked about fertility. Improved counselling for women in the middle to later stages of their reproductive lives might be possible with a more accurate marker of oocyte number and quality. Consequently, we set out to evaluate the link between AMH and spontaneously conceived pregnancies[13].

Many recent research have looked at how AMH levels relate to adverse pregnancy outcomes (e.g., the relationship with pre-eclampsia or preterm births) [14-16]. Yarde *et al.* [15] revealed that AMH levels are considerably lower in women with a history of pre-eclampsia compared to women with normotensive pregnancies [15]. These findings provide credence to the hypothesis that decreased vascular health is a causal factor in premature ovarian ageing, as preeclampsia is a symptom of vascular dysfunction. It has been found in other research that a woman's reproductive potential is more strongly influenced by her biological age than her chronological age. Oocyte number can be accurately predicted by measuring AMH, a new marker of ovarian reserve[17].

It was the goal of this work to determine the association between AMH and miscarriage among women naturally conceived pregnancy.

SUBJECTS AND METHODS
Subjects:
This study was undertaken in the period between June 2021 to December 2021 in the Obstetrics and Gynecology Department at Fetomaternal Unit in Zagazig University Hospital, 40 pregnant women aged from 20 to 35 years old with mean 26.8±4.01 years at gestational age ranged between 6-8 weeks who were trying to conceive naturally were included in the study.

The inclusion criteria were: Patients of first trimester threatened miscarriage presented with vaginal bleeding or spotting, gestational age ranged between 6-8 weeks by history of last menstrual period (LMP) and confirmed by ultrasound, and single living fetus. However, women were not included if they reported body mass index (BMI) $\geq$ 30 kg/m^2, history of polycystic ovarian syndrome (PCOs), pregnancy after induction of ovulation or assisted reproductive technology ART, multiple gestation, anembryonic pregnancy (blighted ovum), presence of local (gynecological) disease such as fibroid or adnexal masses confirmed by normal appearance of the uterus and ovaries by ultrasound; history of general medical disease such as diabetes, thyroid disease, or antiphospholipid syndrome. Recurrent miscarriage is a reliable indicator of uterine anomalies like hypoplastic uterus or septate uterus, hysterosalpingography or 3D transvaginal ultrasonograph was performed, and exposure to local trauma (Abdominal or sexual) were not included in the study.

Ethical consent:
Zagazig University's Research Ethics Council approved the study as long as all participants signed informed consent forms and submitted them to ZU-IRB#6981. We adhered to the Helsinki Declaration, which is the ethical norm for human testing established by the World Medical Association.
This is what all of the participants in this research had to go through:

Full history: Personal, menstrual, contraceptive and obstetric history.
Clinical examination: General examination, abdominal examination and pelvic examination were done.

Transvaginal Ultrasound (TVUS)
Laboratory investigations: Complete blood count (CBC), INR, PT, PTT, SGOT, SGPT, serum creatinine, fasting and postprandial blood sugar and urine analysis.

Serum AMH measurement:
The patients' serum samples were collected and frozen at -20°C until AMH level is assayed by the AMH Gen II ELISA Kit for the quantitative detection of AMH.

Assessing the likelihood of a miscarriage or pregnancy:
The women participated by completing a baseline questionnaire on their demographics, health, and reproductive histories as well as lifestyle factors like caffeine consumption. When a participant in the study saw a positive pregnancy test, they were to inform the researchers. Between 6 and 8 weeks of pregnancy, an endovaginal ultrasound was planned for all patients to check the expected delivery date and fetal viability.
Women who participated in the study and were pregnant were asked to fill out an outcome survey after giving birth. The miscarriage date and dilatation and curettage (D and C) status were two questions asked of women who reported having a miscarriage. Women who did not report a miscarriage between 20 and 24 weeks of pregnancy were contacted to verify the pregnancy's viability and collect new contact information.

Statistical analysis
In order to analyze the data acquired, Statistical Package for the Social Sciences version 20 was used to execute it on a computer (SPSS). In order to convey the findings, tables and graphs were employed. The quantitative data were presented in the form of the mean, median, standard deviation, range and interquartile range. Receiver Operating Characteristic (ROC) curve analysis: The diagnostic performance of a test, or the accuracy of a test to discriminate diseased cases from non-diseased cases is evaluated using

Receiver Operating Characteristic (ROC) curve analysis. Sensitivity and Specificity were detected from the curve and PPV, NPV and accuracy were calculated through cross tabulation. The information was presented using qualitative statistics such as frequency and percentage. The significance of a P value of 0.05 or less was determined.

RESULTS

Table (1) shows that the mean age of the studied cases was 26.8 years while that of BMI was 25.8 kg/m². 80% of the studied cases were multipara, however, 15% of patients had a previous history of miscarriage.

Table (1): Demographic data of the studied cases

Variable	(n = 40)	
Age (yr)		
Mean ± SD	26.8±4.01	
Range	20 - 35	
BMI (kg/m²)		
Mean ± SD	25.80±3.24	
Range	18.5-30	
Variable	No	%
Parity:		
Primipara	8	20
Multipara	32	80
Prior miscarriages:		
Yes	6	15.0
No	34	85.0

Mean Anti-Müllerian hormone (AMH) among the studied cases was 2.41 ng/ml **(Table 2).**

Table (2): Anti- Müllerian hormone level among the study group

Anti-Müllerian level (ng/ml)	(n = 40)
Mean ± SD	2.41±0.52
Median (IQR)	2.55 (1.53-3.2)

AMH levels were shown to increase with age in a way that was statistically significant and statistical +ve significant correlation were found between AMH and gestational sac size, crown lump length, yolk sac size and fetal heart rate among the studied cases **(Table 3).**

Table (3): Correlation between AMH and different parameters among the studied cases

Variable	AMH (n = 40)	
	r	p
Age (years)	-0.39	0.01*
BMI (Kg/m²)	0.19	0.25 NS
Gestational age (weeks)	0.12	0.48 NS
Number of prior live births	0.01	0.99 NS
Gestational sac size (mm)	**0.35**	**0.02***
Crown lump length (mm)	**0.38**	**0.01***
Yolk sac (mm)	**0.36**	**0.03***
Fetal heart rate (beat/min)	**0.34**	**0.04***

There was a statistical significant decrease in AMH among cases had LBW and preterm labor compared to other cases **(Table 4).**

Table (4): Relation between AMH and final pregnancy outcome among female completed pregnancy

Variable	No	AMH Mean ± SD	MW	P value
Outcome:				
Normal pregnancy	21	2.9 ± 0.61		
IUFD	3	2 ± 0.42		
Low birth weight (LBW)	4	2.9 ± 0.46	10.03	0.03*
Preeclampsia	2	3.35 ± 0.57		
Preterm labor	3	1.8 ± 0.32		

AMH at cut off <1.9 ng/ml had sensitivity 85.7%, specificity 87.9% and accuracy 87.5% in prediction of early pregnancy loss among the studied cases **(Table 5, Figure 1).**

Table (5): Validity of AMH and in predication of early pregnancy loss among the studied cases

Variable	Cut off	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC (95%CI)	P
AMH	<1.9	85.7%	87.9%	87.5%	60%	96.7%	0.95(0.88-1)	<0.001**
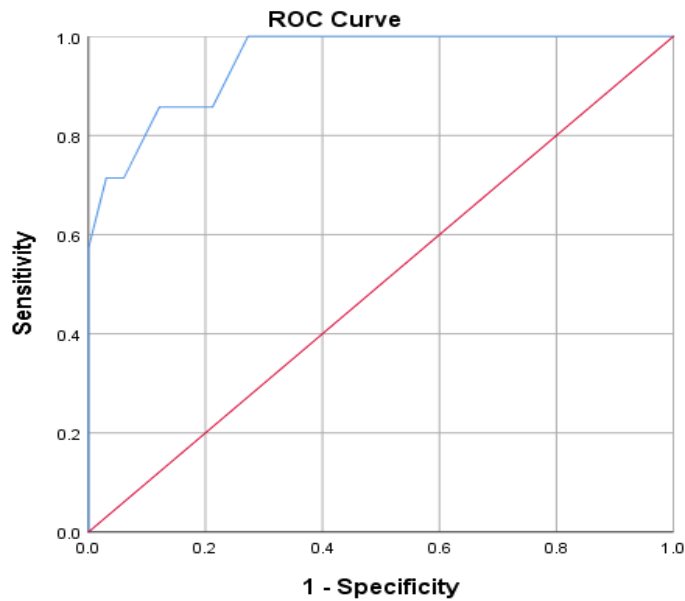
Figure (1): Validity of AMH and in predication of early pregnancy loss among the studied cases.

AMH at cut off <2.75 ng/ml had sensitivity 66.7%, specificity 57.1% and accuracy 63.6% in prediction of unfavorable pregnancy outcome among the studied cases **(Table 6, Figure 2).**

Table (6): Validity of AMH and in predication of unfavorable pregnancy outcome among the studied cases

Variable	Cut off	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC (95%CI)	P
AMH	<2.75	66.7%	57.1%	63.6%	50%	80%	0.62 (0.42-0.83)	0.25 NS
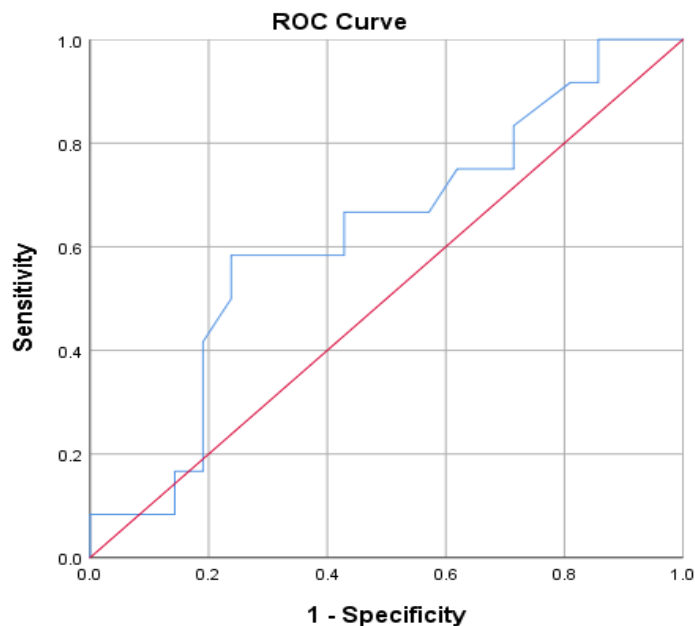
Figure (2): Validity of AMH and in predication of pregnancy complications among the studied cases

DISCUSSION

Bleeding that occurs in the uterus during pregnancy but does not fulfil the diagnostic criteria for a spontaneous abortion is considered a threatening miscarriage. The cervix remains closed during a threatened abortion. In the early half of pregnancy, without cervical dilatation, the World Health Organization (WHO) considers bloody vaginal discharge or frank bleeding to be a cause for concern. Abdominal pain and/or bleeding during early pregnancy may signal a threatened abortion [18].

Serum and ultrasound methods have both been explored extensively for their ability to act as reliable markers of ovarian reserve in infertile patients. However, a reliable indicator of oocyte quality remains elusive. The granulosa cells in the pre-antral and early antral follicles release a hormone called anti-müllerian hormone (AMH). Age-related decreases in AMH are consistent with its function as a measure of oocyte quantity [19]. Oocyte yield after controlled ovarian hyperstimulation, as well as menopausal age, can be predicted using AMH[20].

Studies in a patient with spontaneous pregnancy are needed to show if there is any association between AMH and pregnancy outcome in patients with threating miscarriage. This study is the first of its kind to examine the link between AMH and miscarriage in women who conceived their babies through natural means, and it may have important implications for reducing the risk of miscarriage and other difficulties during these pregnancies.

In light of this, the current study hypothesized that women with decreased AMH would have an increased risk of unfavorable pregnancy outcomes in patients with threatened miscarriage when conceiving spontaneously.

The current study was conducted on 40 women aged from 20 to 35 years with mean 26.8 years. As regard, BMI between them ranged from 18.5 to 30 kg/m² with mean 25.8 kg/m². However, a majority of 27.5% patients had positive family history of previous miscarriage, 7.5% had endometriosis and 12.5% had chronic pelvic infections. According to demographic characteristics data, our data confirmed the Egyptian study of **Elkafrawy and Ahmed** [21] who conducted their study on pregnant women aged from 20 to 40 years with gestational age ranged from 6 to 10 weeks, the mean BMI was 23.80±3.84 kg/m² and it ranged from 17.4 to 30 kg/m². In contrast those patients didn't have family history of miscarriage, some of their family had endometriosis and chronic pelvic infections.

The current study examined gestational age of pregnant women at first time of examination, which ranged from 6 to 8 weeks. Regarding previous obstetric history 15% had previous history of miscarriage, 80 % had previous livebirths, 75% of previous deliveries were by CS. Finally, majority of

17.5% had complication in previous pregnancies (2.5% IUFD, followed 5% preterm labor and 10% preeclampsia). These findings agreed with the study of **Ticconi** *et al.* [22] and **Wang** *et al.* [23]. Several other studies, however, found none of the aforementioned causes and effects of miscarriage [24, 25].

According to the role of Anti-Müllerian hormone (AMH) in predicting the outcome of threatened miscarriage in naturally conceived pregnancies, the current study revealed that, the mean AMH was 2.41 ng/ml and median was 2.55 ng/ml and it ranged from 0.8 to 4 ng/ml. In the study of **Schumacher** *et al.* [26] very low AMH (0.4 ng/ml) was related with an increased risk of miscarriage in women who conceived naturally and had no history of infertility. Reduced ovarian reserve has been linked to an increased incidence of miscarriage in some studies of infertile women [27-29]. One previous study showed that women over the age of 34 years with an AMH in the 20th percentile (≤ 1.6 ng/mL) had a two-fold increase in miscarriage rate compared to women with an AMH >1.6 ng/mL [30].

Regarding the correlation between AMH levels and different parameters, the current study demonstrated a statistical –ve significant correlation between AMH and age and statistical +ve significant correlation between AMH and gestational sac size, crown lump length, yolk sac size and fetal heart rate among the studied cases. These findings were in accordance with the study of **Umarsingh** *et al.* [31].

Regarding the relation between AMH and clinical history among the studied group, the current study demonstrated a statistically significant decrease in AMH among cases had endometriosis, cases had previous history of miscarriage and among cases had severe vaginal bleeding. These findings were in accordance with the study of **Umarsingh** *et al.* [31].

Regarding the relation between AMH levels and pregnancy continuation, the current study demonstrated a statistically significant decrease in AMH among cases had aborted before 20 weeks compared to cases completed pregnancy. The study of **Umarsingh** *et al.* [31], included 120 pregnant women, Group 1 had a mean serum AMH value of 1.58 ng/ml, and 21 out of 34 pregnant women (61.76%) in that group miscarried before 20 weeks. Out of the 26 women who became pregnant in Group 2, 15.38 percent (4/26; P .0<5) experienced a spontaneous abortion and the average serum AMH was 3.74. Therefore, lower serum AMH concentrations were seen in patients who aborted before 20 weeks gestation, suggesting a link between AMH levels and the risk of spontaneous abortion (p <0.05). Like our study, **Schumacher** *et al.* [26], found that very low AMH (<0.4 ng/ml) was related with a greater risk of miscarriage in women who conceived naturally and had no history of infertility.

Regarding the relation between AMH and final pregnancy outcome, the current study revealed that 63.6% of the cases completed pregnancy had normal pregnancy outcome while 36.4% had complications (IUFD 9.1%, LBW 12.1%, preeclampsia 12.1% and preterm labor 9.1%). Additionally, the study demonstrated a statistically significant decrease in AMH among cases had LBW and preterm labor compared to other cases. These findings were in agreement with the study of **Umarsingh** *et al.* **(31)**, Twenty-one of the thirty-four pregnant women in Group 1 (61.76 percent) were reported to have terminated their pregnancies before 20 weeks (mean serum AMH value: 1.58 ng/ml). The average serum AMH in the 13 women (38.23%) who carried to term was 3.33 ng/ml. In contrast, of the 26 women in group 2 who became pregnant, 4 (15.38%) had a spontaneous abortion and 22 (84.61%) sustained the pregnancy into 20 weeks, with a mean serum AMH of 3.74 and 5.24, respectively.

Regarding the validity of AMH levels in predication of early pregnancy loss and in predication of unfavorable pregnancy outcome, the current study demonstrated that, AMH at cut off <1.9 ng/ml had sensitivity 85.7%, specificity 87.9% and accuracy 87.5% in prediction of early pregnancy loss among the studied cases. Moreover, AMH at cut off <2.75 ng/ml had sensitivity 66.7%, specificity 57.1% and accuracy 63.6% in prediction of unfavorable pregnancy outcome among the studied cases.

The meta-analysis of **Lin** *et al.* **(32)**, included studies used a range of cut off values for AMH detection, from 0.75 ng/ml to 2 ng/ml. This led to the presentation of the threshold effect, a negative relationship between sensitivity and specificity. We drew the ROC curve to make sure we weren't exaggerating the results of our experiments. When the AUC was 0.5 to 0.7, the predictive value was low; when it was 0.7 to 0.9, it was good; and when it was >0.9, it was excellent. Weak predictive ability was indicated by an AUC of 0.5932 and a Q index of 0.5702.

This study found that both AMH levels and age were significant predictors of miscarriage. Although maternal age is a well-established predictor of miscarriage, we also factored in anti-Mullerian hormone (AMH) to provide more nuanced predictions of risk for premature pregnancy loss[33].

CONCLUSION
Our findings imply that miscarriage risk is higher in pregnancies conceived without artificial means. Because of its correlation with miscarriage, low AMH or lower ovarian reserve may be a sign of impaired reproductive capacity.

Conflict of interest: The authors declare no conflict of interest.

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